Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSPTALAB1643

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

```
 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09  ACD predicted properties enhanced in REGISTRY/ZREGISTRY
 NEWS  4  OCT 03  MATHDI removed from STN
 NEWS  5  OCT 04  CA/CAplus-Canadian Intellectual Property Office (CIPO) added
                  to core patent offices
 NEWS  6  OCT 13  New CAS Information Use Policies Effective October 17, 2005
 NEWS  7  OCT 17  STN(R) AnaVist(TM), Version 1.01, allows the export/download
                  of CAplus documents for use in third-party analysis and
                  visualization tools
 NEWS  8  OCT 27  Free KWIC format extended in full-text databases
 NEWS  9  OCT 27  DIOGENES content streamlined
 NEWS 10  OCT 27  EPFULL enhanced with additional content
 NEWS 11  NOV 14  CA/CAplus - Expanded coverage of German academic research
 NEWS 12  NOV 30  REGISTRY/ZREGISTRY on STN(R) enhanced with experimental
                  spectral property data
 NEWS 13  DEC 05  CASREACT(R) - Over 10 million reactions available
 NEWS 14  DEC 14 2006 MeSH terms loaded in MEDLINE/LMEDLINE
 NEWS 15  DEC 14 2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
 NEWS 16  DEC 14 CA/CAplus to be enhanced with updated IPC codes
 NEWS 17  DEC 16 MARPATprev will be removed from STN on December 31, 2005
 NEWS 18  DEC 21 IPC search and display fields enhanced in CA/CAplus with the
                 IPC reform
 NEWS 19  DEC 23 New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/USPAT2

 NEWS EXPRESS  DECEMBER 02 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 02 DECEMBER 2005.
               V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
               http://download.cas.org/express/v8.0-Discover/

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)
```

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

```
FILE 'HOME' ENTERED AT 10:47:36 ON 29 DEC 2005

=> file medl, caplus, biosis, embase, wpids
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.42       0.42

FILE 'MEDLINE' ENTERED AT 10:48:31 ON 29 DEC 2005

FILE 'CAPLUS' ENTERED AT 10:48:31 ON 29 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 10:48:31 ON 29 DEC 2005
Copyright (c) 2005 The Thomson Corporation

FILE 'EMBASE' ENTERED AT 10:48:31 ON 29 DEC 2005
Copyright (c) 2005 Elsevier B.V. All rights reserved.

FILE 'WPIDS' ENTERED AT 10:48:31 ON 29 DEC 2005
COPYRIGHT (C) 2005 THE THOMSON CORPORATION

=> s (antibod? or human? b cell) and (glycosylat? or hcn1 or hcn2 or hcn3 or hcn4
or hcn5)
L1       26767 (ANTIBOD? OR HUMAN? B CELL) AND (GLYCOSYLAT? OR HCN1 OR HCN2 OR
               HCN3 OR HCN4 OR HCN5)

=> s L1 and (Fc constant or (heavy or light) (w) chain)
L2         873 L1 AND (FC CONSTANT OR (HEAVY OR LIGHT) (W) CHAIN)

=> s L2 and ch1
L3          20 L2 AND CH1

=> s L2 and hll2
L4           4 L2 AND HLL2

=> s L3 or L4
L5          24 L3 OR L4

=> dup rem L5
PROCESSING COMPLETED FOR L5
L6          20 DUP REM L5 (4 DUPLICATES REMOVED)

=> d IBIB ABS

L6   ANSWER 1 OF 20  WPIDS  COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER:     2005-630946 [64]   WPIDS
DOC. NO. CPI:         C2005-189316
TITLE:                New composition comprising a xenotypic antibody
                      fragment, useful for eliciting a T-cell response against
                      hepatitis B virus and hepatitis C virus infections.
DERWENT CLASS:        B04 D16
INVENTOR(S):          GEORGE, R; NOUJAIM, A; TYRRELL, L; WANG, D
PATENT ASSIGNEE(S):   (VIRE-N) VIREXX RES INC
COUNTRY COUNT:        108
PATENT INFORMATION:

     PATENT NO        KIND DATE     WEEK      LA   PG
     ---------------------------------------------
     WO 2005087813    A1 20050922 (200564)* EN  143
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE
            LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
```

DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG
US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005087813	A1	WO 2004-IB373	20040214

PRIORITY APPLN. INFO: WO 2004-IB373 20040214
AN 2005-630946 [64] WPIDS
AB WO2005087813 A UPAB: 20051006
NOVELTY - A new composition for eliciting a T cell response which comprises contacting an antigen presenting cell with a chimeric antigen comprising an immune response domain and a target binding domain, which comprises a xenotypic **antibody** fragment.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a method of enhancing antigen presentation in antigen presenting cells;
(2) a method of activating antigen presenting cells;
(3) a method of eliciting a T cell response; and
(4) a method for producing a chimeric antigen in an insect cell expression system.
ACTIVITY - Virucide.
No biological data given.
MECHANISM OF ACTION - Vaccine.
USE - The composition is useful for eliciting a T-cell response against hepatitis B virus and hepatitis C virus infections.
Dwg.0/56

=> d 2-20 IBIB ABS

L6 ANSWER 2 OF 20 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-591987 [60] WPIDS
DOC. NO. CPI: C2005-178431
TITLE: Preparing an immunotoxin for diagnosing or treating, for e.g. cancer or infection, comprises culturing a mammalian host cell transformed with nucleic acid sequences encoding fusion proteins containing recombinant cytotoxic RNAses.
DERWENT CLASS: B04 D16
INVENTOR(S): CHANG, C; GOLDENBERG, D M; HANSEN, H J; ROSSI, E A; VANAMA, S
PATENT ASSIGNEE(S): (IMMU-N) IMMUNOMEDICS INC
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005080586	A1	20050901	(200560)*	EN	56

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005080586	A1	WO 2005-US4860	20050214

PRIORITY APPLN. INFO: US 2004-544227P 20040213
AN 2005-591987 [60] WPIDS
AB WO2005080586 A UPAB: 20050920
NOVELTY - Preparing an immunotoxin comprising culturing a mammalian host cell transformed with nucleic acid sequences encoding fusion proteins containing recombinant cytotoxic RNAses, is new.

DETAILED DESCRIPTION - Preparing an immunotoxin comprising culturing a mammalian host cell, where the host cell is transformed with a first nucleic acid sequence encoding a fusion polypeptide, where the fusion polypeptide comprises a non-mammalian ribonuclease fused to a first immunoglobulin variable domain, and a second nucleic acid sequence encoding a second polypeptide comprising a second immunoglobulin variable domain, where the first and second immunoglobulin variable domains together form an antigen binding site.

INDEPENDENT CLAIMS are also included for:

(1) an immunotoxin comprising:

(a) a fusion polypeptide, where the fusion protein comprises a non-mammalian ribonuclease fused to a first immunoglobulin variable domain; and

(b) a second polypeptide comprising a second immunoglobulin variable domain, where one of the immunoglobulin variable domains is a **light chain** variable domain and the other immunoglobulin variable domain is a **heavy chain** variable domain, where the first and second immunoglobulin variable domains together form an antigen binding site, and where the immunotoxin is **glycosylated** ; or an immunotoxin comprising an internalizing **antibody** or **antibody** fragment fused to a cytotoxic RNAse moiety, where the cytotoxic RNAse moiety bears an N-terminal pyroglutamate residue and is fused at its C-terminus to the N-terminus of a polypeptide comprising the **light chain** of the **antibody** or **antibody** fragment, and where the **antibody** or **antibody** fragment comprises separate light and heavy chains;

(2) a pharmaceutical composition comprising the above immunotoxin and a pharmaceutical carrier; and

(3) treating a disease or syndrome in a subject.

ACTIVITY - Cytostatic; Antimicrobial; Immunosuppressive.

No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The methods and composition are useful for diagnosing, preventing or treating diseases or syndromes associated with unwanted or inappropriate cell proliferation or activation, such as cancer, infection or autoimmune disorders.

Dwg.0/13

L6 ANSWER 3 OF 20 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-555933 [56] WPIDS
DOC. NO. CPI: C2005-167492
TITLE: Production of immunoglobulin involves expressing in vertebrate host cell of furin family endoprotease activity fusion polypeptide having secretion targeting sequence, polypeptide sequences, and cleavage site(s) for endoprotease activity.
DERWENT CLASS: B04 D16
INVENTOR(S): GAY, R; KALLMEIER, R; KALWY, S; REISS, G
PATENT ASSIGNEE(S): (LONZ) LONZA LTD
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005075514	A2	20050818	(200556)*	EN	54

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005075514	A2	WO 2005-EP2538	20050310

PRIORITY APPLN. INFO: US 2004-600775P 20040812; US 2004-551353P 20040310; US 2004-554914P 20040322

AN 2005-555933 [56] WPIDS

AB WO2005075514 A UPAB: 20050902

NOVELTY - Immunoglobulin is produced by expressing in a vertebrate host cell having Golgi-only or late-Golgi-only resident furin family endoprotease activity an fusion polypeptide comprising a secretion targeting sequence directing the polypeptide to the secretory pathway and first and second polypeptide sequences and cleavage site(s) for the endoprotease activity.

DETAILED DESCRIPTION - Production of immunoglobulin (Ig) involves expressing in a vertebrate host cell having Golgi-only or late-Golgi-only resident furin family endoprotease activity an fusion polypeptide comprising a secretion targeting sequence directing the polypeptide to the secretory pathway and further comprising the first and second polypeptide sequences and cleavage site(s) for the endoprotease activity; having the fusion polypeptide cleaved in the cells by the furin family endoprotease activity into the first and second polypeptide chain; and harvesting the secreted immunoglobulin. The immunoglobulin has Fc receptor activity and/or complement activation activity, which immunoglobulin molecule when secreted from the vertebrate host cell having the first and second polypeptide chain, in which two polypeptide chains are different.

An INDEPENDENT CLAIM is also included for host cell for producing the immunoglobulin. The host cell is provided for expressing Golgi-only or late Golgi-only resident furin family endoprotease activity and further expressing a fusion polypeptide comprising a secretion targeting sequence directing the polypeptide to the endoplasmic reticulum and the secretory pathway for secretion to the extracellular space, which fusion polypeptide comprises the first and second polypeptide sequences and cleavage site(s) for the endoprotease activity.

USE - For producing immunoglobulin (claimed).

ADVANTAGE - The inventive method is capable of removing partially or completely linker portions from the N-terminus of variable domain to avoid inhibitory effects of linker segments on the binding of an antigen to an **antibody** that is specific for the antigen. It allows for improved expression levels of the fused and endoproteolytically cleaved separate two chain heterodimeric expression of **antibody** in the given host cell.

Dwg.0/1

L6 ANSWER 4 OF 20 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-506603 [51] WPIDS

CROSS REFERENCE: 2005-506604 [51]

DOC. NO. CPI: C2005-153784

TITLE: New **antibody** or its antigen-binding fragment that binds specifically and with high affinity to **glycosylated** and non-**glycosylated** human interleukin-13 (IL-13), useful for treating IL-13-mediated disorders, such as asthma and eczema.

DERWENT CLASS: B04 D16

INVENTOR(S): FUNG, S C; HUANG, D; LU, M; MOYLE, M; SINGH, S; YAN, C

PATENT ASSIGNEE(S): (TANO-N) TANOX INC

COUNTRY COUNT: 108

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005062967	A2	20050714	(200551)*	EN	129

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005062967	A2	WO 2004-US43501	20041223

PRIORITY APPLN. INFO: US 2003-532130P 20031223

AN 2005-506603 [51] WPIDS

CR 2005-506604 [51]

AB WO2005062967 A UPAB: 20050810

NOVELTY - An **antibody** or its antigen-binding fragment that binds specifically and with high affinity to **glycosylated** and non-**glycosylated** human interleukin-13 (IL-13), does not bind mouse IL-13, and neutralizes human IL-13 activity at an approximate molar ratio of 1:2 (MAb:IL13), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) an **antibody** that binds to the same epitope as the **antibody** cited above;

(2) an **antibody** comprising antigen binding regions derived from the light and **heavy chain** variable regions of the novel **antibody**;

(3) a hybridoma cell line that produces a monoclonal **antibody** selected from 228B/C-1, 228A-4, 227-26, and 227-43 and designated with the ATCC deposit number PTA-5657, PTA-5656, PTA-5654, and PTA-5655, respectively;

(4) a cell line comprising a nucleic acid encoding the **antibody**;

(5) a vector comprising the nucleic acid encoding the **antibody**;

(6) a composition comprising the **antibody** and a physiologically acceptable carrier, diluent, excipient, or stabilizer;

(7) a variable **light chain** region comprising an amino acid sequence having the formula: FRL1-CDRL1-FRL2-CDRL2-FRL3-CDRL3-FRL4;

(8) a variable **heavy chain** region comprising an amino acid sequence having the formula: FRH1-CDRH1-FRH2-CDRH2-FRH3-CDRH3-FRH4;

(9) an **antibody** or its antigen binding fragment comprising the variable light or **heavy chain** region, where the **antibody** binds specifically to IL-13;

(10) treating a subject suffering from asthmatic symptoms comprising administering an **antibody** to reduce the asthmatic symptoms;
(11) an inhalation device that delivers the **antibody** to a patient;
(12) detecting interleukin-13 protein in a sample;
(13) diagnosing overexpression of IL-13 in a subject;
(14) producing the **antibody**;
(15) a recombinant **antibody** molecule, or an IL-13-binding fragment, comprising: at least one **antibody heavy chain**, or an IL-13-binding fragment, comprising non-human CDRs at positions 31-35 (CDR1), 50-65 (CDR2) and 95-102 (CDR3) (Kabat numbering) from a mouse anti-IL-13 **antibody**, where positions 27-30 have the amino acid Gly 26, Phe 27, Ser 28, Leu 29, Asn 30; and at least one **antibody light chain**, or an IL-13-binding fragment, comprising non-human CDRs at positions 24-34 (CDR1), 50-56 (CDR2) and 89-97 (CDR3) from a mouse anti-IL13 **antibody** and framework regions from a monoclonal **antibody**;
(16) a DNA sequence encoding the recombinant **antibody**;
(17) a vector comprising the DNA sequence;
(18) a host cell comprising the vector;
(19) inhibiting IgE **antibody** production in a patient;
(20) treating an IL-13-mediated disorder in a patient;
(21) reducing the severity of asthma in a mammal; and
(22) a peptide consisting essentially of the amino acid sequence Glu-Ser-Leu-Ile-Asn-Val-Ser-Gly (SEQ ID Number 18), or Tyr-Cys-Ala-Ala-Leu-Glu-Ser-Leu-Ile-Asn-Val-Ser (SEQ ID Number 19), given in the specification.
ACTIVITY - Antiasthmatic; Antiinflammatory; Dermatological; Antiallergic; Respiratory-Gen.; Antiulcer; Gastrointestinal-Gen.; Ophthalmological; Osteopathic; Virucide.
No biological data given.
MECHANISM OF ACTION - **Antibody** therapy.
USE - The **antibody** and methods are useful for treating IL-13-mediated disorders, such as allergic asthma, non-allergic (intrinsic) asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, eczema, urticaria, food allergies, chronic obstructive pulmonary disease, ulcerative colitis, RSV infection, uveitis, scleroderma, or osteoporosis (claimed).
Dwg.0/21

L6 ANSWER 5 OF 20 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-758278 [74] WPIDS
DOC. NO. CPI: C2004-266126
TITLE: New immunogenic recombinant **antibody** comprising a part of a murine IgG2a subtype amino acid sequence and a mammalian **glycosylation**, useful in preparing a vaccine for immunizing primates against infectious or autoimmune disorders.
DERWENT CLASS: B04 D16
INVENTOR(S): HIMMLER, G; LOIBNER, H; PUTZ, T; SCHUSTER, M; WAXENECKER, G
PATENT ASSIGNEE(S): (IGEN-N) IGENEON KREBS IMMUNTHERAPIE FORSCHUNGS
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004091655	A2	20041028	(200474)*	EN	59

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004091655	A2	WO 2004-EP4059	20040416

PRIORITY APPLN. INFO: AT 2003-599 20030417
AN 2004-758278 [74] WPIDS
AB WO2004091655 A UPAB: 20041117
NOVELTY - A new immunogenic recombinant **antibody** designed for immunization of primates comprises at least a part of a murine IgG2a subtype amino acid sequence and a mammalian **glycosylation**.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) a vaccine comprising the **antibody** in a pharmaceutical formulation;
(2) a multicistronic **antibody** expression construct for producing an **antibody** in a Chinese Hamster Ovary (CHO) or HEK293 expression system, which contains at least a nucleotide sequence encoding a kappa **light chain** and a nucleotide sequence encoding a gamma **heavy chain**, where at least one of the nucleotide sequences encoding a kappa **light chain** or gamma **heavy chain** comprises a nucleotide sequence encoding at least a part of a murine IgG2a subtype amino acid sequence, and at least two IRES elements;
(3) a vector comprising a promoter, the **antibody**-expression construct and a transcription termination sequence;
(4) a CHO host cell or a HEK 293 transformed with the vector; and
(5) a method of producing an **antibody**.
ACTIVITY - Antimicrobial; Immunosuppressive.
No biological data given.
MECHANISM OF ACTION - Vaccine.
USE - The immunogenic recombinant **antibody** is useful in preparing a vaccine for immunizing primates against infectious or autoimmune disorders.
Dwg.0/10

L6 ANSWER 6 OF 20 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-070718 [07] WPIDS
CROSS REFERENCE: 2005-090628 [10]
DOC. NO. CPI: C2004-029232
TITLE: New composition comprises contacting an antigen presenting cell with a chimeric antigen comprising an immune response and a target binding domains, useful for eliciting an immune response and for treating chronic viral infections.
DERWENT CLASS: B04 D16
INVENTOR(S): GEORGE, R; NOUJAIM, A; TYRRELL, L
PATENT ASSIGNEE(S): (GEOR-I) GEORGE R; (NOUJ-I) NOUJAIM A; (TYRR-I) TYRRELL L
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2004001853	A1	20040101 (200407)*			137

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2004001853	A1	Provisional	US 2002-390564P	20020620
		Provisional	US 2002-423578P	20021105

PRIORITY APPLN. INFO: US 2003-365620 20030213; US
2002-390564P 20020620; US
2002-423578P 20021105
AN 2004-070718 [07] WPIDS
CR 2005-090628 [10]
AB US2004001853 A UPAB: 20050211
NOVELTY - A new composition for eliciting a T-cell response in vivo comprises contacting an antigen presenting cell with a chimeric antigen comprising an immune response domain (IRD) and a target binding domain (TBD).

DETAILED DESCRIPTION - IRD comprises one or more sequences comprising:

(i) HBV core protein, HBV S protein, HBV S1 protein, HBV S2 protein or any of its combinations or recombinant molecules;

(ii) DHBV core protein, DHBV Pre-S protein, DHBV Pre/S protein or any of its combinations or recombinant molecules; or

(iii) HCV Core (1-191) protein, HCV Core (1-177) protein, HCV E1 protein, HCV E2 protein, HCV E1-E2 protein, HCV NS5A protein or any of its combinations or recombinant molecules and where TBD comprises a xenotypic **antibody** fragment.

INDEPENDENT CLAIMS are also included for:

(1) enhancing antigen presentation in antigen presenting cells;

(2) activating antigen presenting cells;

(3) eliciting a T cell response; and

(4) producing a chimeric antigen in an insect cell expression system.

ACTIVITY - Immunostimulant; Antiinflammatory; Hepatotropic; Virucide; Cytostatic; Immunosuppressive. No biological data given.

MECHANISM OF ACTION - Vaccine.

USE - The composition is useful in enhancing antigen presentation in antigen, activating antigen-presenting cells or eliciting a T cell response, TH1 or TH2 response. The composition is useful in eliciting immune responses against chronic Hepatitis B infections in animals and humans. The composition is useful in treating chronic viral infections as Hepatitis B or C, Human Immunodeficiency Virus, Human Papilloma Virus, Herpes Simplex Virus, cancer or autoimmune disorders.

Dwg.0/58

L6 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:656213 CAPLUS
DOCUMENT NUMBER: 139:196293
TITLE: Compositions and methods to generate multi-functional target-binding proteins
INVENTOR(S): Hoogenboom, Henricus Renerus Jacobus Mattheus
PATENT ASSIGNEE(S): Dyax Corporation, Neth.
SOURCE: U.S. Pat. Appl. Publ., 34 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003157091	A1	20030821	US 2003-364815	20030211
PRIORITY APPLN. INFO.:			US 2002-357294P P	20020214

AB The disclosed invention relates to generation of functional target-binding proteins from at least two sep. polypeptide chains, one including the target-binding domain, the other including an effector domain. For example, the two sep. chains are reconstituted as a functional protein by a non-covalent binding interaction mediated by an interaction sequence or by intein-mediated ligation. A method is described for preparation of

polypeptides starting from nucleic acids. A first nucleic acid (NA) is constructed that encodes the VH and **CH1** domains of a particular **antibody**, the c-fos zipper, and a hexa-histidine tag. The first NA is expressed in the same bacterial cell as a second NA encoding the **antibody light chain** and Fab fragments are purified from the bacterial periplasm. A third NA is constructed that encodes a hexa-histidine tag, the c-jun zipper, the hinge domain, and the CH2 and CH3 domains of IgG1. This NA is expressed in a mammalian cell. The purified Fab and effector domains are combined and tested for cell-mediated cytotoxicity against cells that express the antigen.

L6 ANSWER 8 OF 20 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-854481 [79] WPIDS
DOC. NO. CPI: C2003-241137
TITLE: New **antibody** fragments, useful for treatment and diagnosis of tumors, that recognize **glycosylated** carcino-embryonal antigens.
DERWENT CLASS: B04 D16
INVENTOR(S): ACEVEDO CASTRO, B E; AYALA AVILA, M; BELL GARCIA, H; CREMATA ALVAREZ, J A; FREYRE ALMEIDA, F D L M; GAVILONDO COWLEY, J V; GONZALEZ LOPEZ, L J; MONTESINO SEGUI, R; ROQUE NAVARRO, L T; ALVAREZ, J A C; AVILA, M A; CASTRO, B E A; COWLEY, J V G; DE LOS MILAGROS FREYRE, ALMEID; GARCIA, H B; LOPEZ, L J G; NAVARRO, T L R; SEGUI, R M; AYALA VILA, M; DE LOS MILAGROS FREYRE, A; FREYRE ALMEIDA, F M; ALMEIDA, F D L M; GAILONDO, C J V; NAVARRO, L T R
PATENT ASSIGNEE(S): (INGG-N) CENT ING GENETICA & BIOTECNOLOGIA; (ALME-I) ALMEIDA F D L M F; (ALVA-I) ALVAREZ J A C; (AVIL-I) AVILA M A; (CAST-I) CASTRO B E A; (GAIL-I) GAILONDO C J V; (GARC-I) GARCIA H B; (LOPE-I) LOPEZ L J G; (NAVA-I) NAVARRO L T R; (SEGU-I) SEGUI R M
COUNTRY COUNT: 104
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003093315	A2	20031113	(200379)*	ES	49
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003223831	A1	20031117	(200442)		
BR 2003004649	A	20040720	(200451)		
EP 1505076	A2	20050209	(200512)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
KR 2005007376	A	20050117	(200535)		
US 2005158322	A1	20050721	(200548)		
MX 2004010695	A1	20050301	(200568)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003093315	A2	WO 2003-CU5	20030428
AU 2003223831	A1	AU 2003-223831	20030428
BR 2003004649	A	BR 2003-4649	20030428
		WO 2003-CU5	20030428
EP 1505076	A2	EP 2003-720119	20030428
		WO 2003-CU5	20030428
KR 2005007376	A	KR 2004-717674	20041029

US 2005158322	A1	WO 2003-CU5	20030428
		US 2005-511794	20050317
MX 2004010695	A1	WO 2003-CU5	20030428
		MX 2004-10695	20041028

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2003223831	A1	Based on	WO 2003093315
BR 2003004649	A	Based on	WO 2003093315
EP 1505076	A2	Based on	WO 2003093315
MX 2004010695	A1	Based on	WO 2003093315

PRIORITY APPLN. INFO: CU 2002-86 20020429

AN 2003-854481 [79] WPIDS

AB WO2003093315 A UPAB: 20031208

NOVELTY - **Antibody** fragments (A) of the monomeric, single-chain Fv type, obtained from the RNA of the hybridoma that produces monoclonal **antibody** CB/ior-CEA.1, specific for human carcino-embryonal antigen (CEA), in soluble form, adsorbed on solid surfaces or present in cells, are new. (A) has affinity constant for **glycosylated** CEA of 5 plus or minus 0.4 multiply 109 1/mole.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) similar divalent (diabody) fragment (A2) with affinity constant for **glycosylated** CEA of 2.8 plus or minus 0.3 multiply 1010 1/mole;

(2) CEA-specific recombinant or synthetic **antibody** fragments (B) containing the variable heavy and **light chain** regions of (A) and (A2), artificially linked as Fab or other scFv fragments, bispecific **antibodies** or fused to biologically or biochemically active domains;

(3) cells or multicellular organisms that express (A), (A2) or (B); and

(4) vectors that encode (A), (A2) or (B).

ACTIVITY - Cytostatic.

No biological data given.

MECHANISM OF ACTION - **Antibody** binding to CEA.

USE - (A), and related diabodies (A2), optionally labeled, are used to identify tumor cells that express CEA. Also (A), (A2) and other **antibody** structures containing the same variable domains, are used, optionally in conjunction with an active agent, for treatment or in vivo localization (imaging) of CEA-expressing tumors, e.g. of colon, lung or breast.

ADVANTAGE - (A) are related fragments retain high affinity for CEA and do not cross-react with normal human tissues or cells (except normal colonic mucosa, where CEA is occasionally present). Since they are smaller, by a factor of 2.5-5 times, than the complete **antibody**, they have better tissue penetration and are less immunogenic in humans.

Dwg.0/5

L6 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2003:442595 CAPLUS
DOCUMENT NUMBER:	139:228923
TITLE:	Characterization of serum immunoglobulin M of the Antarctic teleost Trematomus bernacchii
AUTHOR(S):	Pucci, Biagio; Coscia, Maria Rosaria; Oreste, Umberto
CORPORATE SOURCE:	CNR, Institute of Protein Biochemistry, Naples, 80125, Italy
SOURCE:	Comparative Biochemistry and Physiology, Part B: Biochemistry & Molecular Biology (2003), 135B(2), 349-357 CODEN: CBPBB8; ISSN: 1096-4959
PUBLISHER:	Elsevier Science Inc.

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Trematomus bernacchii IgM concentration was determined in the serum by ELISA; the mean concentration value was 2.7 mg/mL corresponding to 9.6% of the total serum proteins. Purified IgM was analyzed by SDS-PAGE, isoelectrofocusing and 2D electrophoresis. The relative mol. mass of the polymeric form was 830 kDa; that of separated H and L chains was, resp., 78 and 25 kDa. The isoelec. points of the entire mol. ranged from 4.4 to 6.5, that of isolated H chains was between 4.0 and 6.0. Separated H chains were shown to reaggregate in tetrameric form. The cleavage site of trypsin was at the end of the **CH1** domain, as confirmed by the N-terminal amino acid sequence of one of the resultant peptides. Immunoblotting was used to detect carbohydrates in the H and L chains labeled with digoxigenin. Glycosyl residues were detected only in the H chain. The carbohydrate content was evaluated to be 12.8% of the entire chain. Purified Igs were hydrolyzed by N-glycosidase F at different conditions and at least four different hydrolytic sites were revealed by limited deglycosylation. T. bernacchii IgM was also compared to those of five other polar fish species.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 20 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:597114 BIOSIS
DOCUMENT NUMBER: PREV200200597114
TITLE: Construction and functional analysis of a whole human IgG **antibody** against Candida mannan.
AUTHOR(S): Zhang, M. X. [Reprint author]; Parren, P. W.; Itatani, C. [Reprint author]; Adeseun, A.; Nyeche, C.; Kozel, T. R.
CORPORATE SOURCE: California State University, Long Beach, CA, USA
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2002) Vol. 102, pp. 211-212. print. Meeting Info.: 102nd General Meeting of the American Society for Microbiology. Salt Lake City, UT, USA. May 19-23, 2002. American Society for Microbiology. ISSN: 1060-2011.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Nov 2002
Last Updated on STN: 20 Nov 2002
AB Appreciable amounts of anti-Candida mannan **antibodies** are present in sera from normal individuals without regard to gender, race, and age. However, the significance and biological functions of natural antimannan **antibodies** are poorly understood. One approach to this question is to generate recombinant human anti-Candida **antibodies**. The purpose of this study was to convert a recombinant antimannan Fab (M1) to a full length IgG1 **antibody** with an expression vector pIgG1. M1 VL-CL gene was subcloned into pIgG1 and M1 VH-**CH1** gene was ligated with the gene for the constant domains of the IgG1 **heavy chain** contained in pIgG1. Stoichiometric expression of the light and **heavy chain** genes is under separate control of a human cytomegalovirus promoter/enhancer. Whole **antibody** molecules were produced with a Chinese hamster ovarian cell line and purified with protein A. The IgG1 subclass identity of the **antibody** was confirmed with an IgG1-specific monoclonal **antibody** by ELISA. The whole IgG1 **antibody** retained the mannan-binding specificity of M1 as determined in ELISA with chemically purified mannan as the antigen and was subsequently defined as M1g1. M1g1 was reactive with a broad spectrum of Candida species as revealed by immunofluorescence microscopy. In functional analysis, M1g1 was found to mediate deposition of complement C3 fragments to Candida yeast cells in a dose dependent manner, suggesting

that the **antibody** was properly **glycosylated**. Furthermore, M1g1 enhanced both ingestion/binding of Candida yeast cells by human monocyte-derived macrophages and phagocytic killing of the yeast by human neutrophils in a dose-dependent manner, indicating an involvement of Fc and Fc-receptor interactions. Thus, M1g1 appears to be the first functional recombinant human **antibody** reactive with Candida mannan.

L6 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:587489 CAPLUS
DOCUMENT NUMBER: 137:336368
TITLE: Plasma cell dyscrasia-related renal diseases
AUTHOR(S): Meier, Pascal; Mougenot, Beatrice; Aucouturier, Pierre; Ronco, Pierre
CORPORATE SOURCE: Laboratoire d'immunologie, hopital Tenon, Inserm U. 489, Paris, F-75020, Fr.
SOURCE: Hematologie (2002), 8(2), 129-140
CODEN: HEMAF2; ISSN: 1264-7527
PUBLISHER: John Libbey Eurotext
DOCUMENT TYPE: Journal; General Review
LANGUAGE: French
AB A review. The spectrum of renal diseases with deposition or precipitation of monoclonal Ig related material is wide, and such a diversity is probably due to unusual physicochem. properties of the secreted Ig. These properties account for recurrence of the initial renal disease after transplantation and for correlations between the type of renal lesions induced in mice injected with human nephritogenic light chains and the initial nephropathy. Since the first description of myeloma casts, considerable progress has been made in the understanding of the pathophysiol. of Ig related renal diseases. In myeloma cast nephropathy, filtered light chains bind to a peptidic segment of nine amino acids of the Tamm-Horsfall glycoprotein (THP) (probably through a sequence in their CDR3 loop), and their interaction triggers cast formation in the distal nephron where THP is produced. The proximal tubular lesions seen in κ chain Fanconi's syndrome (FS) are characterized by crystal formation. Fanconi's syndrome light chains are remarkable for restricted usage of two VκI genes with unusual amino-acid substitutions, and for resistance of the variable domain Vκ to proteolysis. Not all light chains are amyloidogenic but the following characteristics are predisposing factors: λ isotype, VλVI variability subgroup, unusual substitution by acid amino acids in the variable region Vλ, and tendency to dimerize. At variance with amyloidosis, lesions in monoclonal Ig deposition disease are characterized by a dramatic accumulation of extracellular matrix. **Light chain** deposition disease is characterized by predominance of κ chains, abnormal **glycosylation** that occurs in about 20% of patients and is correlated with very low circulating **light chain** levels, and presence in CDR1 loop of hydrophobic residues that might increase the **light chain** propensity to precipitate in tissues. In the recently described **heavy chain** deposition disease, the nephritogenic **heavy chain** is remarkable for the deletion of the **CH1** domain. However, **CH1** deletion seems necessary but not sufficient for deposition, and it is likely that the VH also contributes to tissue deposition. Some of the above physicochem. properties open new therapeutic avenues for the treatment of plasma cell dyscrasia-related renal diseases.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 20 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-465958 [40] WPIDS
DOC. NO. CPI: C2000-140353
TITLE: New nucleic acid encoding a fusion protein comprising a signal sequence, an immunoglobulin Fc region and a target

protein sequence with leptin for treating obesity, diabetes, hypertension, heart disease and cancer.

DERWENT CLASS: B04 C06 D16
INVENTOR(S): GILLIES, S D; LO, K; ZHANG, J
PATENT ASSIGNEE(S): (LEXI-N) LEXIGEN PHARM CORP
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000040615	A2	20000713	(200040)*	EN	56
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2000026025	A	20000724	(200052)		
NO 2001003371	A	20010904	(200161)		
EP 1141013	A2	20011010	(200167)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
BR 2000007414	A	20011016	(200170)		
CZ 2001002406	A3	20020313	(200223)		
HU 2001005090	A2	20020429	(200238)		
CN 1341121	A	20020320	(200246)		
KR 2002007287	A	20020126	(200252)		
ZA 2001005352	A	20020828	(200264)		70
JP 2002534962	W	20021022	(200301)		73
SK 2001000943	A3	20030204	(200318)		
MX 2001006922	A1	20020501	(200368)		
US 2004053366	A1	20040318	(200421)		
AU 778939	B2	20041223	(200510)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000040615	A2		WO 2000-US352	20000107
AU 2000026025	A		AU 2000-26025	20000107
NO 2001003371	A		WO 2000-US352	20000107
			NO 2001-3371	20010706
EP 1141013	A2		EP 2000-904239	20000107
			WO 2000-US352	20000107
BR 2000007414	A		BR 2000-7414	20000107
			WO 2000-US352	20000107
CZ 2001002406	A3		WO 2000-US352	20000107
			CZ 2001-2406	20000107
HU 2001005090	A2		WO 2000-US352	20000107
			HU 2001-5090	20000107
CN 1341121	A		CN 2000-804274	20000107
KR 2002007287	A		KR 2001-708580	20010706
ZA 2001005352	A		ZA 2001-5352	20010628
JP 2002534962	W		JP 2000-592323	20000107
			WO 2000-US352	20000107
SK 2001000943	A3		WO 2000-US352	20000107
			SK 2001-943	20000107
MX 2001006922	A1		WO 2000-US352	20000107
			MX 2001-6922	20010706
US 2004053366	A1	Provisional	US 1999-115079P	19990107
		Cont of	US 2000-479508	20000107
			US 2003-419058	20030418
AU 778939	B2		AU 2000-26025	20000107

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000026025	A	Based on	WO 2000040615
EP 1141013	A2	Based on	WO 2000040615
BR 2000007414	A	Based on	WO 2000040615
CZ 2001002406	A3	Based on	WO 2000040615
HU 2001005090	A2	Based on	WO 2000040615
JP 2002534962	W	Based on	WO 2000040615
SK 2001000943	A3	Based on	WO 2000040615
MX 2001006922	A1	Based on	WO 2000040615
AU 778939	B2	Previous Publ.	AU 2000026025
		Based on	WO 2000040615

PRIORITY APPLN. INFO: US 1999-115079P 19990107; US
2000-479508 20000107; US
2003-419058 20030418

AN 2000-465958 [40] WPIDS

AB WO 200040615 A UPAB: 20021105

NOVELTY - A nucleic acid encoding a fusion protein comprising a signal sequence, an immunoglobulin Fc region and a target protein sequence comprising leptin, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a replicable expression vector for transfecting a mammalian cell, comprising the new nucleic acid;

(2) a mammalian cell harboring the new nucleic acid;

(3) a fusion protein comprising an immunoglobulin Fc region and a target protein comprising leptin, where the fusion protein, administered at a dose of about 0.25 mg/kg/day for 5 days to an ob (obesity)/ob mouse with an initial body weight of 50 grams, induces a 10 % or 5 gram loss in body weight;

(4) a multimeric protein comprising at least two fusion proteins of (3), linked via a covalent bond;

(5) producing a fusion protein of (3) comprising culturing the mammalian cell of (2); and

(6) treating a condition alleviated by the administration of leptin comprising administering the new nucleic acid, the vector of (1), the fusion protein of (3), or the multimeric protein of (4).

ACTIVITY - Anorectic. The fusion proteins when administered by injection at a dose of 0.1 mg/kg/day for 5 days to an ob/ob mouse having an initial body weight of 50 grams, induce a 10 % (5 gram) loss of the initial body weight (claimed).

MECHANISM OF ACTION - Gene therapy. No biological data is given.

USE - The new nucleic acid, vector comprising it, fusion protein and multimeric protein are used to treat a condition that is alleviated by the administration of leptin (claimed), such as obesity. Diabetes, hypertension, heart disease, cancer and other related disorders can be treated. **Antibodies** can be produced, using the nucleic acid, for diagnostic uses. Fc-leptins derived from other mammals, e.g., bovine and porcine are used for raising lean animals for meat.

ADVANTAGE - The fusion proteins can facilitate high level expression of biologically active anti-obesity proteins.

Dwg.0/7

L6 ANSWER 13 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2000308160 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10849371
TITLE: The amino acid sequence of a monoclonal gamma 3-**heavy chain** from a patient with articular gamma-**heavy chain** deposition disease.
AUTHOR: Danevad M; Sletten K; Gaarder P I; Mellbye O J; Husby G
CORPORATE SOURCE: Department of Biochemistry/Biotechnology Center of Oslo,

Norway.
SOURCE: Scandinavian journal of immunology, (2000 Jun) 51 (6) 602-6.
Journal code: 0323767. ISSN: 0300-9475.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000714
Last Updated on STN: 20000714
Entered Medline: 20000706

AB Abnormal deposition of proteins, including monoclonal immunoglobulin gamma-heavy chains, may cause tissue damage and organ dysfunction. We here report the amino acid sequence of the free gamma-heavy chains present in serum and urine of the first reported case (patient G. L.) of synovial **heavy chain** deposition disease. The protein was heavily deleted and consisted of the hinge, in addition to the CH2 and CH3 domains, in a dimeric form, thus lacking its variable domain as well as the **CH1** domain. The sequence was consistent with the gamma 3 subclass (gamma 3GL). Gm typing revealed the gamma 3 allotypes G3m(b0) and G3m(b1) in accordance with the residues Pro123, Phe128, Thr171 and Phe268 in gamma 3GL. Furthermore, the gamma 3GL molecule was **glycosylated** at Asn in position 129. Finally, the gamma 3GL protein was shown to contain a typical binding site for the first complement component, C1q, namely the residues Glu150, Lys152 and Lys154, with the potential of binding and activating complement, causing tissue damage following deposition.

L6 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:691228 CAPLUS
DOCUMENT NUMBER: 131:321542
TITLE: Chimeric immunoglobulins containing CH domains of IgA
INVENTOR(S): Morrison, Sherie L.; Chintalacharuvu, Koteswara R.; Yoo, Esther Mikyung; Trinh, Kham M.; Coloma, M. Josefina
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9954484	A1	19991028	WO 1999-US8647		19990420
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
AU 9936558	A1	19991108	AU 1999-36558		19990420
US 6284536	B1	20010904	US 1999-295283		19990420
PRIORITY APPLN. INFO.:			US 1998-82578P	P	19980420
			US 1998-96085P	P	19980811
			WO 1999-US8647	W	19990420

AB The authors disclose the preparation of modified Ig mols. using exon exchange. In one example, the modified **antibody** in IgG2 and contains a CH3

domain of an IgA mol. (α CH3). The combination of an α CH3 with other domains selected from one or more non-IgA **antibodies** provides for an Ig mol. that has the capacity to bind J chain and/or secretory component together with features of a non-IgA **antibody** . The modified Igs can also contain a **CH1** and/or a CH2 domain of an IgA mol. The combination of an α **CH1** and/or a CH2 domain with other domains selected from one or more non-IgA **antibodies** provides for the capacity to form higher polymers (trimers, tetramers, pentamers, etc.). The chimeric **antibodies** can also be engineered to lack one or more carbohydrate addition sites.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:550444 CAPLUS
DOCUMENT NUMBER: 129:174688
TITLE: Stimulation of an immune response with **antibodies** labeled with the α-galactosyl epitope
INVENTOR(S): Leung, Shui-On; Qu, Zhengxing
PATENT ASSIGNEE(S): Immunomedics, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9834957	A1	19980813	WO 1998-US1976	19980206
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9860543	A1	19980826	AU 1998-60543	19980206
EP 1007569	A1	20000614	EP 1998-903896	19980206
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6090381	A	20000718	US 1998-20299	19980206
JP 2001512438	T2	20010821	JP 1998-534822	19980206
US 6472511	B1	20021029	US 2000-599391	20000623

PRIORITY APPLN. INFO.: US 1997-37908P P 19970211
US 1998-20299 A3 19980206
WO 1998-US1976 W 19980206

AB The authors disclose a method for stimulation of humoral and cellular immune responses against tumor cells and infectious agents using an **antibody** that contains at least one α-galactosyl epitope. Such an **antibody** is capable of forming a complex with cells that express the target epitope and with xenoreactive **antibodies** that bind α-galactosyl epitopes. Suitable **antibodies** include mols. that contain at least one engineered **glycosylation** site in the constant region of the **heavy chain**.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 16 OF 20 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-479995 [44] WPIDS
CROSS REFERENCE: 1998-447170 [38]
DOC. NO. CPI: C1997-152443

TITLE: Monoclonal **antibody** engineered to contain **glycosylation** site - in non-**Fc** **constant** heavy or **light chain** region, useful to diagnose or treat B cell malignancies, e.g. non-Hodgkins lymphoma.

DERWENT CLASS: B04 D16

INVENTOR(S): HANSEN, H; LEUNG, S; QU, Z; HANSEN, H J

PATENT ASSIGNEE(S): (IMMU-N) IMMUNOMEDICS INC; (HANS-I) HANSEN H; (LEUN-I) LEUNG S; (QUZZ-I) QU Z

COUNTRY COUNT: 77

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9734632	A1	19970925	(199744)*	EN	88
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU					
AU 9725318	A	19971010	(199806)		
EP 888125	A1	19990107	(199906)	EN	
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI					
AU 705063	B	19990513	(199930)		
JP 2000507818	W	20000627	(200036)		73
US 6254868	B1	20010703	(200140)		
US 2003035800	A1	20030220	(200316)		
EP 888125	B1	20040526	(200435)	EN	
R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI					
DE 69729283	E	20040701	(200443)		
US 2004258682	A1	20041223	(200504)		
DE 69729283	T2	20050525	(200537)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9734632	A1		WO 1997-US4196	19970319
AU 9725318	A		AU 1997-25318	19970319
EP 888125	A1		EP 1997-916787	19970319
			WO 1997-US4196	19970319
AU 705063	B		AU 1997-25318	19970319
JP 2000507818	W		JP 1997-533585	19970319
			WO 1997-US4196	19970319
US 6254868	B1	Provisional	US 1996-13709P	19960320
			WO 1997-US4196	19970319
			US 1998-155107	19981117
US 2003035800	A1	Provisional	US 1996-13709P	19960320
		Cont of	WO 1997-US4196	19970319
		Cont of	US 1998-155107	19981117
			US 2001-894839	20010629
EP 888125	B1		EP 1997-916787	19970319
			WO 1997-US4196	19970319
DE 69729283	E		DE 1997-629283	19970319
			EP 1997-916787	19970319
			WO 1997-US4196	19970319
US 2004258682	A1	Provisional	US 1996-13709P	19960320
		Cont of	WO 1997-US4196	19970319
		Cont of	US 1998-155107	19981117
		Cont of	US 2001-894839	20010629
			US 2004-787378	20040227
DE 69729283	T2		DE 1997-629283	19970319

EP 1997-916787 19970319
WO 1997-US4196 19970319

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9725318	A	Based on	WO 9734632
EP 888125	A1	Based on	WO 9734632
AU 705063	B	Previous Publ.	AU 9725318
		Based on	WO 9734632
JP 2000507818	W	Based on	WO 9734632
US 6254868	B1	Based on	WO 9734632
US 2003035800	A1	Cont of	US 6254868
EP 888125	B1	Based on	WO 9734632
DE 69729283	E	Based on	EP 888125
		Based on	WO 9734632
US 2004258682	A1	Cont of	US 6254868
DE 69729283	T2	Based on	EP 888125
		Based on	WO 9734632

PRIORITY APPLN. INFO: US 1996-13709P 19960320; US
1998-155107 19981117; US
2001-894839 20010629; US
2004-787378 20040227

AN 1997-479995 [44] WPIDS
CR 1998-447170 [38]
AB WO 9734632 A UPAB: 20050613
Monoclonal **antibody** (MAb), or a fragment, engineered to contain a **glycosylation** site in the non-**Fc constant** heavy or **light chain** region, is claimed. Also claimed is an isolated DNA molecule comprising: (a) Ab **heavy chain** gene, comprising a sequence in the **CH1** region that, when the gene is coexpressed with a gene for an Ab **light chain** in a cell supporting **glycosylation**, will produce an Ab **glycosylated** in the **CH1** region; or (b) Ab **light chain** gene, comprising a sequence in the constant K region that, when the gene is coexpressed with a gene for an Ab **heavy chain** in a cell supporting **glycosylation** , will produce an Ab **glycosylated** in the constant K region.

USE - The MAb (preferably humanised), or a fragment, can be used to diagnose or treat of B cell malignancies, e.g. non-Hodgkins lymphoma or chronic lymphocytic leukaemia.

ADVANTAGE - The **glycosylation** site allows a label or therapeutic agent of increased size to be conjugated to the carbohydrate moiety, without affecting the MAb's binding affinity or specificity.

Dwg.0/12

L6 ANSWER 17 OF 20 MEDLINE on STN
ACCESSION NUMBER: 1998054111 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9393962
TITLE: **Glycosylation** is influential in murine IgG3 self-association.
AUTHOR: Panka D J
CORPORATE SOURCE: Department of Microbiology, Boston University Medical School, MA 02118, U.S.A.
SOURCE: Molecular immunology, (1997 Jun) 34 (8-9) 593-8. Journal code: 7905289. ISSN: 0161-5890.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980122

Last Updated on STN: 19980122
Entered Medline: 19980105

AB In mice and humans, **antibodies** of the IgG3 isotype are unique in that they spontaneously self-associate. A consequence is the formation of cryoglobulins from some, but not all IgG3 molecules. Little is known about the structural basis of murine IgG3 self-association. A region of the CH3 domain that is unique to IgG3 **antibodies** is the presence of an extra **glycosylation** site at residues 471-473. It is known that **glycosylation** greatly influences solubility. It has also been shown by X-ray crystallography that **glycosylated** residues (specifically sialic acid) are influential in the contacts of the **CH1** to CH2 as well as the CH2 to CH2 domains in a human IgG1 **antibody**. These findings provided evidence that a direct interaction exists between the **glycosylated** residues and other residues within the constant and/or variable domains. It was, therefore, important to determine whether the **glycosylated** residue in the CH3 domain of the IgG3 constant region is influential in self-association. We have found that removing the **glycosylation** site by site-directed mutagenesis of an IgG3 RF significantly reduced the self-associating ability of this **antibody**.

L6 ANSWER 18 OF 20 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 96256892 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8643111
TITLE: Construction and characterization of a humanized, internalizing, B-cell (CD22)-specific, leukemia/lymphoma **antibody**, LL2.
AUTHOR: Leung S O; Goldenberg D M; Dion A S; Pellegrini M C; Shevitz J; Shih L B; Hansen H J
CORPORATE SOURCE: Immunomedics, Inc., Morris Plains, NJ 07950, USA.
CONTRACT NUMBER: CA 39841 (NCI)
SOURCE: Molecular immunology, (1995 Dec) 32 (17-18) 1413-27. Journal code: 7905289. ISSN: 0161-5890.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: PDB-1REI; PDB-3FAB
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 19970203
Entered Medline: 19960715

AB The murine monoclonal **antibody**, LL2, is a B-cell (CD22)-specific IgG2a which has been demonstrated to be clinically significant in the radioimmunodetection of non-Hodgkin's B-cell lymphoma. The **antibody** carries a variable region-appended **glycosylation** site in the **light chain** and is rapidly internalized upon binding to Raji target cells. Humanization of LL2 was carried out in order to develop LL2 as a diagnostic and immunotherapeutic suitable for repeated administration. Based on the extent of sequence homology, and with the aid of computer modeling, we selected the EU framework regions (FR) 1, 2 and 3, and the NEWM FR4 as the scaffold for grafting the **heavy chain** complementarity determining regions (CDRs), and REI FRs for that of light chains. The **light chain** **glycosylation** site, however, was not included. Construction of the CDR-grafted variable regions was accomplished by a rapid and simplified method that involved long DNA oligonucleotide synthesis and the polymerase chain reaction (PCR). The humanized LL2 (**hLL2**), lacking **light chain** variable region **glycosylation**, exhibited immunoreactivities that were comparable to that of chimeric LL2 (cLL2), which was shown previously to have antigen-binding properties similar to its murine counterpart, suggesting that the VK-appended oligosaccharides found in mLL2 are not necessary for antigen binding. Moreover, the **hLL2** retained its ability to be

internalized into Raji cells at a rate similar to its murine and chimeric counterparts.

L6 ANSWER 19 OF 20 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 91032068 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2226804
TITLE: Structural features of the McPC603 Fab fragment not defined in the X-ray structure.
AUTHOR: Skerra A; Glockshuber R; Pluckthun A
CORPORATE SOURCE: Genzentrum der Universitat Munchen, Max-Planck-Institut fur Biochemie, Martinsried, FRG.
SOURCE: FEBS letters, (1990 Oct 1) 271 (1-2) 203-6.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 19910208
Last Updated on STN: 19910208
Entered Medline: 19901204

AB The proteolytic Fab fragment of the well characterized **antibody** McPC603 was compared to the recombinant Fab fragment, which was obtained in functional form from an Escherichia coli expression system [(1989) Methods Enzymol. 178, 497-515]. We found evidence that the proteolytic fragment is **glycosylated** at Asn H160 in the **CH1** domain, where additional electron density had been observed in the crystal structure [J. Mol. Biol. 190, 593-604]. In addition, its **heavy chain** is about 30 amino acids longer than visible in the electron density and thus contains the complete hinge region. These structural differences between the recombinant Fab fragment, which had been designed exactly according to the defined electron density, and the proteolytic Fab fragment of McPC603 had no effect on the hapten binding properties of these antigen binding fragments. Yet, it may be important to be aware of these structural features of McPC603 in folding studies and some comparative analyses of **antibody** structures.

L6 ANSWER 20 OF 20 EMBASE
ACCESSION NUMBER: 81117435 EMBASE
DOCUMENT NUMBER: 1981117435
TITLE: Structural analysis of the μ-chains synthesized by fetal liver hybridomas.
AUTHOR: Kloppel T.M.; Kubo R.T.; Cain P.S.; et al.
CORPORATE SOURCE: Dept. Med., Nat. Jew. Hosp., Denver, Colo. 80206, United States
SOURCE: Journal of Immunology, (1981) Vol. 126, No. 4, pp. 1346-1350.
CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
016 Cancer
LANGUAGE: English
ENTRY DATE: Entered STN: 911209
Last Updated on STN: 911209

AB The existence of the murine fetal liver hybridomas whose Ig phenotype is identical to that of pre-B cells (cytoplasm μ+; cell surface Ig-) has made it possible to study certain structural characteristics associated with the pre-B cell Ig. Previous studies suggested that significant size heterogeneity existed between the μ-chains synthesized by different fetal liver hybridomas. The present study demonstrated that these m.w. differences were apparently not related to different degrees of **glycosylation**, because treatment with tunicamycin did not alter

the observed size variation as determined by SDS gel electrophoresis. Analysis of the cyanogen bromide-generated peptides suggested that the variation did not occur in the Fc fragment and was apparently localized to the V(H) and/or **CH1** domains of the μ-chain. To determine whether the μ-chains synthesized by the pre-B-like hybridomas (i.e., fetal liver hybridomas with the pre-B cell phenotype) were of the secreted or membrane type, the C-terminal structure of the μ-chains was analyzed. Carboxypeptidase-A digestion of purified μ-chains from these hybridomas yielded approximately 1 residue of tyrosine release per μ-chain. These results suggested that the μ-chains synthesized by the pre-B-like hybridomas were of the secreted type, as membrane-type μ-chains failed to release tyrosine under similar conditions of digestion. Furthermore, the C-terminal octapeptide generated by cyanogen bromide cleavage was readily identified in the μ-chains of those pre-B cell hybridomas studied further, indicating that these μ-chains were predominantly of the secreted type.

```
=> s leung s?/au,in; s hansen h?/au,in; s qu z?/au,in
'IN' IS NOT A VALID FIELD CODE
'IN' IS NOT A VALID FIELD CODE
L7         2834 LEUNG S?/AU,IN


'IN' IS NOT A VALID FIELD CODE
'IN' IS NOT A VALID FIELD CODE
L8         7667 HANSEN H?/AU,IN


'IN' IS NOT A VALID FIELD CODE
'IN' IS NOT A VALID FIELD CODE
L9         1779 QU Z?/AU,IN

=> s L7 and L8 and L9
L10          44 L7 AND L8 AND L9

=> s glycosylat? and human? b cell
L11         146 GLYCOSYLAT? AND HUMAN? B CELL

=> s L10 and L11
L12           2 L10 AND L11

=> d bib ab

L12  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   1997:640570  CAPLUS
DN   127:292069
TI   Glycosylated humanized B-cell
     specific antibodies
IN   Leung, Shui-on; Hansen, Hans; Qu, Zhengxing
PA   Immunomedics, Inc., USA; Leung, Shui-On; Hansen, Hans; Qu, Zhengxing
SO   PCT Int. Appl., 87 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
PI   WO 9734632            A1    19970925    WO 1997-US4196          19970319
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ,
             VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
```

RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	CA 2249320	AA	19970925	CA 1997-2249320	19970319
	AU 9725318	A1	19971010	AU 1997-25318	19970319
	AU 705063	B2	19990513		
	EP 888125	A1	19990107	EP 1997-916787	19970319
	EP 888125	B1	20040526		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

	JP 2000507818	T2	20000627	JP 1997-533585	19970319
	AT 267610	E	20040615	AT 1997-916787	19970319
	US 6254868	B1	20010703	US 1998-155107	19981117
	US 2003035800	A1	20030220	US 2001-894839	20010629
	US 2002176856	A1	20021128	US 2002-114315	20020403
	US 2004258682	A1	20041223	US 2004-787378	20040227
PRAI	US 1996-13709P	P	19960320		
	US 1997-37908P	P	19970211		
	WO 1997-US4196	W	19970319		
	US 1998-20299	A3	19980206		
	US 1998-155107	A1	19981117		
	US 2000-599391	A3	20000623		
	US 2001-894839	A1	20010629		

AB A humanized specific monoclonal antibody or antibody fragment, especially a B-cell specific antibody or antibody fragment, is engineered to contain a **glycosylation** site in the non-Fc constant region. The **glycosylated** antibody is useful for diagnosis and/or therapy whenever a targeting antibody or fragment is used, especially for B-cell malignancies. The carbohydrate moiety allows conjugation of labeling or therapeutic agents of increased size, without affecting the binding affinity or specificity of the antibody. Described in the examples were preparation and characterization of **glycosylated**/humanized murine monoclonal antibody LL2 (an IgG2a specific for epitope of CD22 prepared using Raji B lymphoma cell line as source of antigen) and conjugates of the **glycosylated**/humanized antibody and doxorubicin.

=> d bib ab 2

L12 ANSWER 2 OF 2 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2001:367118 BIOSIS
DN PREV200100367118
TI **Glycosylated humanized B-cell** specific antibodies.
AU **Leung, Shui-on** [Inventor]; **Hansen, Hans** [Inventor]; **Qu, Zhengxing** [Inventor]
CS ASSIGNEE: Immunomedics, Inc.
PI US 6254868 20010703
SO Official Gazette of the United States Patent and Trademark Office Patents, (July 3, 2001) Vol. 1248, No. 1. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 2 Aug 2001
Last Updated on STN: 19 Feb 2002
AB A humanized specific monoclonal antibody or antibody fragment, especially a B-cell specific antibody or antibody fragment, is engineered to contain a glyxosylation site in the non-Fc constant region. The **glycosylated** antibody is useful for diagnosis and/or therapy whenever a targeting antibody or fragment is used, especially for B-cell malignancies. The carbohydrate moiety allows conjugation of labeling or therapeutic agents of increased size, without affecting the binding affinity or specificity of the antibody.

=> d bib ab; s L10 not L12

L12 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:640570 CAPLUS
DN 127:292069
TI **Glycosylated humanized B-cell** specific antibodies
IN **Leung, Shui-on; Hansen, Hans; Qu, Zhengxing**
PA Immunomedics, Inc., USA; Leung, Shui-On; Hansen, Hans; Qu, Zhengxing
SO PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9734632	A1	19970925	WO 1997-US4196	19970319
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2249320	AA	19970925	CA 1997-2249320	19970319
	AU 9725318	A1	19971010	AU 1997-25318	19970319
	AU 705063	B2	19990513		
	EP 888125	A1	19990107	EP 1997-916787	19970319
	EP 888125	B1	20040526		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2000507818	T2	20000627	JP 1997-533585	19970319
	AT 267610	E	20040615	AT 1997-916787	19970319
	US 6254868	B1	20010703	US 1998-155107	19981117
	US 2003035800	A1	20030220	US 2001-894839	20010629
	US 2002176856	A1	20021128	US 2002-114315	20020403
	US 2004258682	A1	20041223	US 2004-787378	20040227
PRAI	US 1996-13709P	P	19960320		
	US 1997-37908P	P	19970211		
	WO 1997-US4196	W	19970319		
	US 1998-20299	A3	19980206		
	US 1998-155107	A1	19981117		
	US 2000-599391	A3	20000623		
	US 2001-894839	A1	20010629		

AB A humanized specific monoclonal antibody or antibody fragment, especially a B-cell specific antibody or antibody fragment, is engineered to contain a **glycosylation** site in the non-Fc constant region. The **glycosylated** antibody is useful for diagnosis and/or therapy whenever a targeting antibody or fragment is used, especially for B-cell malignancies. The carbohydrate moiety allows conjugation of labeling or therapeutic agents of increased size, without affecting the binding affinity or specificity of the antibody. Described in the examples were preparation and characterization of **glycosylated**/humanized murine monoclonal antibody LL2 (an IgG2a specific for epitope of CD22 prepared using Raji B lymphoma cell line as source of antigen) and conjugates of the **glycosylated**/humanized antibody and doxorubicin.

L13 42 L10 NOT L12

=> d 1-42 bib ab

L13 ANSWER 1 OF 42 MEDLINE on STN
AN 2000007364 MEDLINE
DN PubMed ID: 10541351
TI The effects of domain deletion, glycosylation, and long IgG3 hinge on the biodistribution and serum stability properties of a humanized IgG1 immunoglobulin, hLL2, and its fragments.
AU **Leung S O**; **Qu Z**; **Hansen H J**; Shih L B; Wang J; Losman M J; Goldenberg D M; Sharkey R M
CS Immunomedics, Inc., Morris Plains, New Jersey 07950, USA.
NC CA 54425 (NCI)
CA39841 (NCI)
SO Clinical cancer research : an official journal of the American Association for Cancer Research, (1999 Oct) 5 (10 Suppl) 3106s-3117s.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124
AB Antibody (Ab) fragments are preferred agents for imaging applications because of their rapid clearance from the blood, thereby providing high tumor:blood ratios within a few hours. Several preclinical studies have also suggested that Ab fragments might be preferred for therapeutic applications over an intact IgG. The purpose of this project was to develop engineered Ab fragments using a humanized anti-carcinoembryonic antigen and anti-CD22 Ab as the parent. Three types of variants were prepared: a deltaCH2 (deletion mutant missing the CH2), a gamma3 F(ab')2 containing the human IgG3 hinge, and three glycosylated variants. The gamma3 F(ab')2 and glycosylated variants were developed because of the potential for site-specific linkage to the Ab in its divalent or monovalent fragment. The gamma3 F(ab')2 variant contains 10 cysteine residues that could be used for direct coupling using thiol chemistry, whereas the glycosylated variants have N-linked glycosylation sites engineered in the CH1 domain (two variants) as well as the VK domain (one variant). All of these variants were successfully prepared and shown to react with the target antigen. All Abs could be purified to a single peak by size-exclusion HPLC, but the deltaCH2 variant showed two distinct peaks, which were believed to be both the divalent and monovalent forms of this fragment. The two CH1 glycosylated variants showed differences in the extent of glycosylation. Modeling studies suggest that one variant would be better suited for site-specific coupling than the other because the carbohydrate chain is extended further away from the antigen-binding site. The Abs were radioiodinated to determine their pharmacokinetic behavior in mice. All of the humanized Ab divalent fragments cleared nearly 20 times faster from the blood than the murine parent F(ab')2 over a 24-h period. The glycosylated fragments showed some added stability compared to the other fragments over 4 h, but by 24 h, they had cleared to the same extent. Size-exclusion high-performance liquid chromatography of blood samples indicated that the humanized Ab fragments were quickly degraded in the blood. Thus, there is an inherent instability of the divalent fragments from these humanized IgG1 constructs that may affect their utility in imaging or therapy applications.

L13 ANSWER 2 OF 42 MEDLINE on STN
AN 2000007363 MEDLINE
DN PubMed ID: 10541350
TI Generation and monitoring of cell lines producing humanized antibodies.
AU Losman M J; **Qu Z**; Krishnan I S; Wang J; **Hansen H J**; Goldenberg D M; **Leung S O**
CS Immunomedics, Inc., Morris Plains, New Jersey 07950, USA.

NC CA 37895 (NCI)
CA 39841 (NCI)
SO Clinical cancer research : an official journal of the American Association for Cancer Research, (1999 Oct) 5 (10 Suppl) 3101s-3105s.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124
AB Antibody humanization has eliminated or reduced the human antimouse antibody response associated with the administration of murine antibodies. We have successfully humanized three different antibodies: (a) hMN-3 (granulocyte targeting); (b) hMu-9 (colorectal cancer targeting); and (c) hWI2 (anti-idiotype to the anti-carcinoembryonic antigen antibody MN-14). All humanized antibodies demonstrated immunoreactivities comparable to their parent counterparts. Previously, we reported the generation of high productivity cell lines for hMN-14 and hLL2 using the amplifiable vector pdHL2. Through amplification, selection, and cloning procedures, cell lines capable of large scale production were established, and further enhancement of production was achieved by a fed-perfusion bioreactor process. Using a similar and improved approach, we have enhanced the production of the above-mentioned humanized antibodies by gene amplification induced by a stepwise increase in the concentration of methotrexate in the culture media. A reliable IgG determination method is essential to monitor amplification, especially at the final cloning stage, for the selection of the subclones with the highest productivity. We found that measurement of humanized IgG concentration in culture media supplemented with more than 1 microM methotrexate by a standard ELISA assay could be unreliable and misleading. Whereas the determination of antibody by adsorption/elution on protein A from a 100-ml culture is accurate and reproducible, the method is time-consuming, tedious, and labor intensive. We have recently developed a Western blot assay that enables us to monitor the productivity of the cultures. The assay is simple and sensitive, and it makes simultaneous determinations of relative antibody production from individual clones at the 96-well stage feasible. With this method, amplification, cloning, and adaptation to serum-free conditions of multiple cell lines can be monitored in an efficient manner.

L13 ANSWER 3 OF 42 MEDLINE on STN
AN 2000007362 MEDLINE
DN PubMed ID: 10541349
TI Humanization of Immu31, an alpha-fetoprotein-specific antibody.
AU **Qu Z**; Losman M J; Eliassen K C; **Hansen H J**; Goldenberg D M; **Leung S O**
CS Immunomedics, Inc., Morris Plains, New Jersey 07950, USA.
NC CA39841 (NCI)
SO Clinical cancer research : an official journal of the American Association for Cancer Research, (1999 Oct) 5 (10 Suppl) 3095s-3100s.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991124
AB Immu31 is a murine monoclonal antibody (Ab) specific for alpha-fetoprotein (AFP), a tumor-associated marker. The excellent tumor targeting ability of Immu31 has led to the development of a Immu31-based

radioimmunodiagnostic agent, AFP-Scan, for hepatocellular carcinoma and other AFP-producing tumors. To enhance the capability of Immu31-based immunoconjugates being used in diagnostic and therapeutic procedures in humans, a humanized version of Immu31 (hImmu31) was constructed by grafting the complementarity determining regions (CDRs) of murine variable domains for the heavy (VH) and kappa (Vkappa) chain to the respective human VH and Vkappa framework regions (FRs). The cDNA encoding the VH and Vkappa of Immu31 was cloned by reverse transcription-PCR from hybridoma cells, and a chimeric Immu31 (cImmu31) composed of murine V and human C domains was constructed. Competitive ELISA assays showed identical AFP binding activity between the chimeric and murine Abs, confirming the authenticity of the cloned V genes. Based on sequence homology, the EU FR1, FR2, and FR3 and the NEWM FR4 were selected as the scaffold for grafting VH CDRs and REI FRs for Vkappa CDRs of Immu31. The amino acid residues in murine FRs that are considered to be in contact with the CDRs of the Ab were maintained in the humanized version. hImmu31, thus constructed and expressed, showed comparable immunoreactivity in a competitive binding ELISA assay to that of murine Immu31 and cImmu31. High-level production was achieved by expressing hImmu31 in a dhfr-based amplifiable system, and the productivity has exceeded 100 mg/liter in terminal cultures.

L13 ANSWER 4 OF 42 MEDLINE on STN
AN 1998355595 MEDLINE
DN PubMed ID: 9692846
TI Carbohydrates engineered at antibody constant domains can be used for site-specific conjugation of drugs and chelates.
AU **Qu Z**; Sharkey R M; **Hansen H J**; Shih L B; Govindan S V; Shen J; Goldenberg D M; **Leung S O**
CS Immunomedics, Morris Plains, NJ 07950, USA.
NC CA39841 (NCI)
SO Journal of immunological methods, (1998 Apr 15) 213 (2) 131-44. Journal code: 1305440. ISSN: 0022-1759.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199808
ED Entered STN: 19980820
Last Updated on STN: 19980820
Entered Medline: 19980813
AB To improve the efficiency of site-specific conjugation of chelates and drugs to antibodies, and to minimize the incidence of immunoreactivity perturbation to the resultant immunoconjugates, Asn-linked oligosaccharide moieties were designed and engineered into the constant domains of a humanized anti-CD22 monoclonal antibody, hLL2. From 10 potential glycosylation mutants, two CH1 domain glycosylation sites, HCN1 and HCN5, were identified that were positioned favorably for glycosylation. The carbohydrate (CHO) chains attached at these sites were differentially processed so that HCN5-CHOs were physically larger than HCN1-CHOs. Although both the CH1-appended CHOs, and the LL2 Vkappa-appended CHOs conjugated efficiently with small chelates, the HCN5-CHOs, due to the structural and positional superiority, appear to be a better conjugation site for large drug complexes, such as 18 kDa doxorubicin (DOX)-dextran.

L13 ANSWER 5 OF 42 MEDLINE on STN
AN 1998068557 MEDLINE
DN PubMed ID: 9406722
TI Generation of a high-producing clone of a humanized anti-B-cell lymphoma monoclonal antibody (hLL2).
AU Losman M J; **Hansen H J**; Dworak H; Krishnan I S; **Qu Z**; Shih L B; Zeng L; Goldenberg D M; **Leung S O**
CS Immunomedics, Inc., Morris Plains, New Jersey 07950, USA.
NC CA 39841 (NCI)

SO Cancer, (1997 Dec 15) 80 (12 Suppl) 2660-6.
Journal code: 0374236. ISSN: 0008-543X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199801
ED Entered STN: 19980122
Last Updated on STN: 19980122
Entered Medline: 19980102
AB BACKGROUND: LL2 is a murine immunoglobulin (Ig)G2a-kappa anti-B-cell monoclonal antibody with proven targeting and therapeutic efficacy in the management of non-Hodgkin's lymphoma (NHL). The authors had previously generated a humanized LL2 (hLL2) that demonstrated binding properties identical to those of LL2. Nevertheless, the productivity of the cell line was insufficient for large-scale production of the antibody for clinical studies. Therefore, the authors chose an amplifiable system for the generation of hLL2. METHODS: The hLL2 sequences were ligated into the expression vector pdHL2, which has a dhfr amplifiable gene, and were incorporated into the SP2/0 cells by electroporation. A methotrexate (MTX) resistant clone producing hLL2 was identified. Stepwise increases in MTX concentrations, from 0.1 to 5 microM, and subcloning of the cells by limiting dilution were performed. RESULTS: By amplifying the dhfr and hLL2 genes with stepwise increases in the MTX concentration, the antibody production was enhanced from its original 1.4 to 70 +/- 5 mg per liter of culture media. Subsequent subcloning further improved the productivity. Immunoreactivity of the antibody was conserved, as proven by enzyme-linked immunosorbent assay and cell-binding assays. By isoelectrofocusing, the isoelectric point (pI) of the antibody was measured at approximately 9.6. The productivity of the clone was not affected by culture conditions or storage of the cells in liquid nitrogen. CONCLUSIONS: By means of gene amplification, the authors have generated a high-producing hLL2-IgG clone suitable for production of the quantity of antibody necessary for clinical diagnostic and therapeutic trials of NHL patients.

L13 ANSWER 6 OF 42 MEDLINE on STN
AN 1998020919 MEDLINE
DN PubMed ID: 9376682
TI Structure determination of N-linked oligosaccharides engineered at the CH1 domain of humanized LL2.
AU **Qu Z**; Sharkey R M; **Hansen H J**; Goldenberg D M; **Leung S**
CS Immunomedics, Inc., Morris Plains, NJ 07950, USA.
NC CA39841 (NCI)
SO Glycobiology, (1997 Sep) 7 (6) 803-9.
Journal code: 9104124. ISSN: 0959-6658.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971110
AB Two humanized antibody mutants, hLL2HCN1 and hLL2HCN5, engineered with CH1 domain-appended carbohydrates (CHOs) were generated to facilitate site-specific conjugation of radionuclides and anti-cancer drugs to antibodies. Such site-specific conjugation may minimize the incidence of immunoreactivity perturbation as is often observed with random conjugation. Since the compositions and structures of CHOs are important in determining the chemistry, efficiency, and extent of conjugation, the sequences of the CH1-appended CHOs were determined by exoglycosidase digestions and fluorophore-assisted CHO electrophoresis (FACE). The CHO species attached at HCN1 and HCN5 sites in hLL2HCN1 and hLL2HCN5,

respectively, were distinct from each other, heterogeneous, and extensively processed. All of these CHOs were core-fucosylated complex-type oligosaccharides and contained Gal (galactose) and GlcNAc (N-acetylglucosamine) residues in the outer branches. Some of the outer branches were composed of Gal alpha1-3Galbeta1-4GlcNAc structure, also known as alpha-galactosyl epitope. Most of the CHOs were sialylated. While all HCN1-CHOs were biantennary, the majority of HCN5-CHOs (>60%) were triantennary. The CH1-appended CHOs have favorable structural characteristics suitable for site-specific conjugation. For efficient conjugation of large drug complexes, hLL2HCN5 is preferable to hLL2HCN1 because the attached CHO is larger in size and more remotely positioned from the V region. The effects of the alpha-galactosyl epitope found in these CHOs on the immunological properties of the immunoconjugates as efficient cancer diagnostics and therapeutics are being studied.

L13 ANSWER 7 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:836381 CAPLUS
DN 139:341719
TI Use of bi-specific antibodies for pre-targeting diagnosis and therapy
IN Goldenberg, David M.; **Hansen, Hans J.**; **Leung, Shui-on**; McBride, William J.; **Qu, Zhengxing**
PA Immunomedics, Inc., USA
SO U.S. Pat. Appl. Publ., 59 pp., Cont.-in-part of U.S. Ser. No. 823,746.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 16

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003198595	A1	20031023	US 2002-150654	20020517
	US 2002006379	A1	20020117	US 2001-823746	20010403
	US 6962702	B2	20051108		
	CA 2486307	AA	20031127	CA 2003-2486307	20030516
	WO 2003097105	A1	20031127	WO 2003-GB2110	20030516
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1506018	A1	20050216	EP 2003-725404	20030516
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	BR 2003010088	A	20050405	BR 2003-10088	20030516
	US 2005002945	A1	20050106	US 2004-776470	20040211
PRAI	US 1998-90142P	P	19980622		
	US 1998-104156P	P	19981014		
	US 1999-382186	A2	19990823		
	US 2001-823746	A2	20010403		
	US 1999-337756	A2	19990622		
	US 2002-150654	A	20020517		
	WO 2003-GB2110	W	20030516		

AB The present invention relates to a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable construct. The targetable construct comprises a carrier portion which comprises or bears at least one epitope recognizable by at least one arm of said bi-specific antibody or antibody fragment. The targetable construct further comprises one or more therapeutic or diagnostic agents or enzymes. The invention provides constructs and methods for producing the

bi-specific antibodies or antibody fragments, as well as methods for using them.

L13 ANSWER 8 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:719519 CAPLUS
DN 139:259963
TI Anti-CD74 antibodies and conjugates for diagnosis and treatment of immune and autoimmune diseases, infections and cancers
IN **Hansen, Hans**; **Leung, Shui-on**; **Qu, Zhengxing**; Goldenberg, David M.
PA Immunomedics, Inc., USA; McCall, John Douglas
SO PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003074567	A2	20030912	WO 2003-GB890	20030303
	WO 2003074567	A3	20031231		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2478012	AA	20030912	CA 2003-2478012	20030303
	EP 1483294	A2	20041208	EP 2003-743421	20030303
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	US 2002-360259P	P	20020301		
	WO 2003-GB890	W	20030303		

AB The present invention provides humanized, chimeric and human anti-CD74 antibodies, CD74 antibody fusion proteins, immunoconjugates, vaccines and bispecific that bind to CD74, the major histocompatibility complex (MHC) class-II invariant chain, Ii, which is useful for the treatment and diagnosis of B-cell disorders, such as B-cell malignancies, other malignancies in which the cells are reactive with CD74, and autoimmune diseases, and methods of treatment and diagnosis.

L13 ANSWER 9 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:51893 CAPLUS
DN 136:123598
TI Production and use of novel peptide-based agents for use with bi-specific antibodies
IN **Hansen, Hans J.**; Griffiths, Gary L.; **Leung, Shui-on**; McBride, William J.; **Qu, Zhengxing**
PA Immunomedics Inc., USA
SO U.S. Pat. Appl. Publ., 37 pp., Cont.-in-part of U. S. Ser. No. 337,756.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 16

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002006379	A1	20020117	US 2001-823746	20010403
	US 6962702	B2	20051108		
	CA 2442839	AA	20021017	CA 2002-2442839	20020403
	WO 2002082041	A2	20021017	WO 2002-US10235	20020403
	WO 2002082041	A3	20030912		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1372718	A2	20040102	EP 2002-725464	20020403
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005503768	T2	20050210	JP 2002-579763	20020403
US 2003198595	A1	20031023	US 2002-150654	20020517
US 2005002945	A1	20050106	US 2004-776470	20040211
US 2005169926	A1	20050804	US 2005-70697	20050303
PRAI US 1998-90142P	P	19980622		
US 1998-104156P	P	19981014		
US 1999-337756	A2	19990622		
US 1999-382186	A2	19990823		
US 2001-823746	A	20010403		
WO 2002-US10235	W	20020403		
US 2002-116116	A3	20020405		
US 2002-150654	A2	20020517		

AB The present invention relates to a bi-specific antibody or antibody fragment having at least one arm that is reactive against a targeted tissue and at least one other arm that is reactive against a linker moiety. The linker moiety encompasses a hapten to which antibodies have been prepared The antigenic linker is conjugated to one or more therapeutic or diagnostic agents or enzymes. The invention provides constructs and methods for producing the bispecific antibodies or antibody fragments, as well as methods for using them.

L13 ANSWER 10 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:819263 CAPLUS
DN 132:69307
TI Use of bispecific antibodies for pre-targeting diagnosis and therapy
IN **Hansen, Hans J.**; Griffiths, Gary L.; **Leung, Shui-On**; McBride, William J.; **Qu, Zhengxing**
PA Immunomedics, Inc., USA
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 16

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9966951	A2	19991229	WO 1999-US13879	19990622
WO 9966951	A3	20000615		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2335364	AA	19991229	CA 1999-2335364	19990622
AU 9945792	A1	20000110	AU 1999-45792	19990622
AU 760854	B2	20030522		
EP 1089766	A2	20010411	EP 1999-928808	19990622
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

	JP 2002518460	T2	20020625	JP 2000-555637	19990622
PRAI	US 1998-90142P	P	19980622		
	US 1998-104156P	P	19981014		
	WO 1999-US13879	W	19990622		

OS MARPAT 132:69307

AB The present invention relates to a bispecific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate. The targetable conjugate comprises a carrier portion which comprises or bears at least one epitope recognizable by at least one arm of said bispecific antibody or antibody fragment. The targetable conjugate further comprises one or more therapeutic or diagnostic agents or enzymes. The invention provides constructs and methods for producing the bispecific antibodies or antibody fragments, as well as methods for using them.

L13 ANSWER 11 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:740242 CAPLUS

DN 132:235679

TI The effects of domain deletion, glycosylation, and long IgG3 hinge on the biodistribution and serum stability properties of a humanized IgG1 immunoglobulin, hLL2, and its fragments

AU **Leung, Shui-on**; **Qu, Zhengxing**; **Hansen, Hans J.** ; Shih, Lisa B.; Wang, Jingrong; Losman, Michele J.; Goldenberg, David M.; Sharkey, Robert M.

CS Immunomedics, Inc., Morris Plains, NJ, 07950, USA

SO Clinical Cancer Research (1999), 5(10, Suppl.), 3106s-3117s
CODEN: CCREF4; ISSN: 1078-0432

PB American Association for Cancer Research

DT Journal

LA English

AB Antibody (Ab) fragments are preferred agents for imaging applications because of their rapid clearance from the blood, thereby providing high tumor:blood ratios within a few hours. Several preclin. studies have also suggested that Ab fragments might be preferred for therapeutic applications over an intact IgG. The purpose here was to develop engineered Ab fragments using a humanized anti-carcinoembryonic antigen and anti-CD22 Ab as the parent. Three types of variants were prepared: a ΔCH2 (deletion mutant missing the CH2), a γ3 F(ab')2 containing the human IgG3 hinge, and 3 glycosylated variants. The γ3 F(ab')2 and glycosylated variants were developed because of the potential for site-specific linkage to the Ab in its divalent or monovalent fragment. The γ3 F(ab')2 variant contains 10 cysteine residues that could be used for direct coupling using thiol chemical, whereas the glycosylated variants have N-linked glycosylation sites engineered in the CH1 domain (2 variants) as well as the VK domain (1 variant). All of these variants were successfully prepared and shown to react with the target antigen. All Abs could be purified to a single peak by size-exclusion HPLC, but the ΔCH2 variant showed 2 distinct peaks, which were believed to be both the divalent and monovalent forms of this fragment. The 2 CH1 glycosylated variants showed differences in the extent of glycosylation. Modeling studies suggest that one variant would be better suited for site-specific coupling than the other because the carbohydrate chain is extended further away from the antigen-binding site. The Abs were radioiodinated to determine their pharmacokinetic behavior in mice. All of the humanized Ab divalent fragments cleared nearly 20 times faster from the blood than the murine parent F(ab')2 over a 24-h period. The glycosylated fragments showed some added stability compared to the other fragments over 4 h, but by 24 h, they had cleared to the same extent. Size-exclusion high-performance liquid chromatog. of blood samples indicated that the humanized Ab fragments were quickly degraded in the blood. Thus, there is an inherent instability of the divalent fragments from these humanized IgG1 constructs that may affect their utility in imaging or therapy applications.

RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:740241 CAPLUS
DN 132:220997
TI Generation and monitoring of cell lines producing humanized antibodies
AU Losman, Michele J.; **Qu, Zhengxing**; Krishnan, Indira S.; Wang, Jingrong; **Hansen, Hans J.**; Goldenberg, David M.; **Leung, Shui-on**
CS Immunomedics, Inc., Morris Plains, NJ, 07950, USA
SO Clinical Cancer Research (1999), 5(10, Suppl.), 3101s-3105s
CODEN: CCREF4; ISSN: 1078-0432
PB American Association for Cancer Research
DT Journal
LA English
AB Antibody humanization has eliminated or reduced the human antimouse antibody response associated with the administration of murine antibodies. We have successfully humanized three different antibodies: (a) hMN-3 (granulocyte targeting); (b) hMu-9 (colorectal cancer targeting); and (c) hWI2 (anti-idiotype to the anti-carcinoembryonic antigen antibody MN-14). All humanized antibodies demonstrated immunoreactivities comparable to their parent counterparts. Previously, we reported the generation of high productivity cell lines for hMN-14 and hLL2 using the amplifiable vector pdHL2. Through amplification, selection, and cloning procedures, cell lines capable of large scale production were established, and further enhancement of production was achieved by a fed-perfusion bioreactor process. Using a similar and improved approach, we have enhanced the production of the above-mentioned humanized antibodies by gene amplification induced by a stepwise increase in the concentration of methotrexate in the culture media. A reliable IgG determination method is essential to monitor amplification, especially at the final cloning stage, for the selection of the subclones with the highest productivity. We found that measurement of humanized IgG concentration in culture media supplemented with more than 1 μM methotrexate by a standard ELISA assay could be unreliable and misleading. Whereas the determination of antibody by adsorption/elution on protein A from a 100-mL culture is accurate and reproducible, the method is time-consuming, tedious, and labor intensive. We have recently developed a Western blot assay that enables us to monitor the productivity of the cultures. The assay is simple and sensitive, and it makes simultaneous detns. of relative antibody production from individual clones at the 96-well stage feasible. With this method, amplification, cloning, and adaptation to serum-free conditions of multiple cell lines can be monitored in an efficient manner.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:740240 CAPLUS
DN 132:221093
TI Humanization of Immu31, an α-fetoprotein-specific antibody
AU **Qu, Zhengxing**; Losman, Michele J.; Eliassen, Kristian C.; **Hansen, Hans J.**; Goldenberg, David M.; **Leung, Shui-on**
CS Immunomedics, Inc., Morris Plains, NJ, 07950, USA
SO Clinical Cancer Research (1999), 5(10, Suppl.), 3095s-3100s
CODEN: CCREF4; ISSN: 1078-0432
PB American Association for Cancer Research
DT Journal
LA English
AB Immu31 is a murine monoclonal antibody (Ab) specific for α-fetoprotein (AFP), a tumor-associated marker. The excellent tumor targeting ability of Immu31 has led to the development of a Immu31-based radioimmunodiagnostic agent, AFP-Scan, for hepatocellular carcinoma and other AFP-producing tumors. To enhance the capability of Immu31-based

immunoconjugates being used in diagnostic and therapeutic procedures in humans, a humanized version of Immu31 (hImmu31) was constructed by grafting the complementarity determining regions (CDRs) of murine variable domains for the heavy (VH) and κ (Vκ) chain to the resp. human VH and Vκ framework regions (FRs). The cDNA encoding the VH and Vκ of Immu31 was cloned by reverse transcription-PCR from hybridoma cells, and a chimeric Immu31 (cImmu31) composed of murine V and human C domains was constructed. Competitive ELISA assays showed identical AFP binding activity between the chimeric and murine Abs, confirming the authenticity of the cloned V genes. Based on sequence homol., the EU FR1, FR2, and FR3 and the NEWM FR4 were selected as the scaffold for grafting VH CDRs and REI FRs for Vκ CDRs of Immu31. The amino acid residues in murine FRs that are considered to be in contact with the CDRs of the Ab were maintained in the humanized version. HImmu31, thus constructed and expressed, showed comparable immunoreactivity in a competitive binding ELISA assay to that of murine Immu31 and cImmu31. High-level production was achieved by expressing hImmu31 in a dhfr-based amplifiable system, and the productivity has exceeded 100 mg/L in terminal cultures.

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 14 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:325973 CAPLUS
DN 130:336967
TI Glycosylated antibodies and antibody fragments having reactive ketone groups
IN **Leung, Shui-On**; McBride, William J.; **Qu, Zhengxing**; **Hansen, Hans**
PA Immunomedics, Inc., USA
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9924472	A2	19990520	WO 1998-US23238	19981106
	WO 9924472	A3	19990805		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002193572	A1	20021219	US 1998-185607	19981104
	US 6953675	B2	20051011		
	CA 2309320	AA	19990520	CA 1998-2309320	19981106
	AU 9913729	A1	19990531	AU 1999-13729	19981106
	AU 757174	B2	20030206		
	EP 1028978	A2	20000823	EP 1998-957482	19981106
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001522864	T2	20011120	JP 2000-520480	19981106
PRAI	US 1997-64386P	P	19971106		
	WO 1998-US23238	W	19981106		

AB The authors disclose methods of making glycosylated antibodies or antibody fragments having reactive ketone groups within the saccharide residues. The method comprises transfecting a cell with a vector encoding an antibody having glycosylation sites engineered within the Vκ or CH1 domains. Culture of the transfecting cells in medium containing a ketone derivative of a saccharide (e.g., N-levulinoyl fucose) or saccharide precursor (e.g., N-levulinoyl mannosamine) allows for biosynthetic incorporation of

the reactive ketone saccharides within the engineered oligosaccharides. In addition, the authors disclose immunoconjugates prepared from the glycosylated antibodies. In one example, the oligosaccharide of engineered ant-CD22 antibodies was conjugated to DTPA derivs. to prepare 111In and 90Y chelates. In a second example, the oligosaccharide of engineered ant-CD22 antibodies was conjugated to doxorubicin.

L13 ANSWER 15 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:380728 CAPLUS
DN 129:153096
TI Carbohydrates engineered at antibody constant domains can be used for site-specific conjugation of drugs and chelates
AU **Qu, Zhengxing**; Sharkey, Robert M.; **Hansen, Hans J.**; Shih, Lisa B.; Govindan, Serengulam V.; Shen, Jian; Goldenberg, David M.; **Leung, Shui-on**
CS Immunomedics, Morris Plains, NJ, 07950, USA
SO Journal of Immunological Methods (1998), 213(2), 131-144
CODEN: JIMMBG; ISSN: 0022-1759
PB Elsevier Science B.V.
DT Journal
LA English
AB To improve the efficiency of site-specific conjugation of chelates and drugs to antibodies, and to minimize the incidence of immunoreactivity perturbation to the resultant immunoconjugates, Asn-linked oligosaccharide moieties were designed and engineered into the constant domains of a humanized anti-CD22 monoclonal antibody, hLL2. From 10 potential glycosylation mutants, two CH1 domain glycosylation sites, HCN1 and HCN5, were identified that were positioned favorably for glycosylation. The carbohydrate (CHO) chains attached at these sites were differentially processed so that HCN5-CHOs were phys. larger than HCN1-CHOs. Although both the CH1-appended CHOs, and the LL2 Vκ-appended CHOs conjugated efficiently with small chelates, the HCN5-CHOs, due to the structural and positional superiority, appear to be a better conjugation site for large drug complexes, such as 18 kDa doxorubicin (DOX)-dextran.
RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:12688 CAPLUS
DN 128:87639
TI Generation of a high-producing clone of a humanized anti-B-cell lymphoma monoclonal antibody (hLL2)
AU Losman, Michele J.; **Hansen, Hans J.**; Dworak, Heather; Krishnan, Indira S.; **Qu, Zhengxing**; Shih, Lisa B.; Zeng, Li; Goldenberg, David M.; **Leung, Shui-On**
CS Immunomedics, Inc., Morris Plains, NJ, 07950, USA
SO Cancer (New York) (1997), 80(12, Suppl.), 2660-2666
CODEN: CANCAR; ISSN: 0008-543X
PB John Wiley & Sons, Inc.
DT Journal
LA English
AB LL2 is a murine IgG2a-κ anti-B-cell monoclonal antibody with proven targeting and therapeutic efficacy in the management of non-Hodgkin's lymphoma (NHL). The authors had previously generated a humanized LL2 (hLL2) that demonstrated binding properties identical to those of LL2. Nevertheless, the productivity of the cell line was insufficient for large-scale production of the antibody for clin. studies. Therefore, the authors chose an amplifiable system for the generation of hLL2. The hLL2 sequences were ligated into the expression vector pdHL2, which has a dhfr amplifiable gene, and were incorporated into the SP2/0 cells by electroporation. A methotrexate (MTX) resistant clone producing hLL2 was identified. Stepwise increases in MTX concns., from 0.1 to 5 μM, and subcloning of the cells by limiting dilution were performed. By amplifying the dhfr and hLL2 genes with stepwise increases in the MTX concentration, the

antibody production was enhanced from its original 1.4 to 70 mg per L of culture media. Subsequent subcloning further improved the productivity. Immunoreactivity of the antibody was conserved, as proven by ELISA and cell-binding assays. By isoelectrofocusing, the isoelec. point (pI) of the antibody was measured at approx. 9.6. The productivity of the clone was not affected by culture conditions or storage of the cells in liquid nitrogen. By gene amplification, the authors have generated a high-producing hLL2-IgG clone suitable for production of the quantity of antibody necessary for clin. diagnostic and therapeutic trials of NHL patients.

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 17 OF 42 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:613785 CAPLUS
DN 127:304935
TI Structure determination of N-linked oligosaccharides engineered at the CH1 domain of humanized LL2
AU **Qu, Zhengxing**; Sharkey, Robert M.; **Hansen, Hans J.**; Goldenberg, David M.; **Leung, Shui-On**
CS Immunomedics, Inc., Morris Plains, NJ, 07950, USA
SO Glycobiology (1997), 7(6), 803-809
CODEN: GLYCE3; ISSN: 0959-6658
PB Oxford University Press
DT Journal
LA English
AB Two humanized antibody mutants, hLL2HCN1 and hLL2HCN5, engineered with CH1 domain-appended carbohydrates (CHOs) were generated to facilitate site-specific conjugation of radionuclides and anticancer drugs to antibodies. Such site-specific conjugation may minimize the incidence of immunoreactivity perturbation as is often observed with random conjugation. Since the compns. and structures of CHOs are important in determining the chemical, efficiency, and extent of conjugation, the sequences of the CH1-appended CHOs were determined by exoglycosidase digestions and fluorophore-assisted CHO electrophoresis (FACE). The CHO species attached at HCN1 and HCN5 sites in hLL2HCN1 and hLL2HCN5, resp., were distinct from each other, heterogeneous, and extensively processed. All of these CHOs were corefucosylated complex-type oligosaccharides and contained Gal (galactose) and GlcNAc (N-acetylglucosamine) residues in the outer branches. Some of the outer branches were composed of Galα1-3Galβ1-4GlcNAc structure, also known as α-galactosyl epitope. Most of the CHOs were sialylated. While all HCN1-CHOs were biantennary, the majority of HCN5-CHOs (>60%) were triantennary. The CH1-appended CHOs have favorable structural characteristics suitable for site-specific conjugation. For efficient conjugation of large drug complexes, hLL2HCN5 is preferable to hLL2HCN1 because the attached CHO is larger in size and more remotely positioned from the V region. The effects of the α-galactosyl epitope found in these CHOs on the immunol. properties of the immunoconjugates as efficient cancer diagnostics and therapeutics are being studied.

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 18 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2000:512977 BIOSIS
DN PREV200000512977
TI Preliminary studies on bispecific antibody pretargeted radioimmunotherapy against human colonic tumor xenografts in mice.
AU **Qu, Z.** [Reprint author]; **Hansen, H. J.** [Reprint author]; Sharkey, R. M.; McBride, W. J. [Reprint author]; Losman, M. J.; Xuan, H. [Reprint author]; Ma, H. [Reprint author]; Chang, C. H. [Reprint author]; Barbet, J.; Goldenberg, D. M.; **Leung, S. O.** [Reprint

author]
CS Immunomedics, Inc., Morris Plains, NJ, 07950, USA
SO Cancer Biotherapy and Radiopharmaceuticals, (2000) Vol. 15, No. 4, pp. 410. print.
Meeting Info.: Eighth Conference on Radioimmunodetection and Radioimmunotherapy of Cancer. Princeton, New Jersey, USA. October 12-14, 2000.
ISSN: 1084-9785.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 22 Nov 2000
Last Updated on STN: 11 Jan 2002

L13 ANSWER 19 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2000:294910 BIOSIS
DN PREV200000294910
TI Pretargeting colonic tumors with engineered bispecific antibodies for improved radioimmunotherapy (RAIT).
AU **Leung, S. O.** [Reprint author]; **Qu, Z.**; Sharkey, R. M.; McBride, W. J.; Losman, M. J.; Chang, C. H.; Barbet, J.; Karacay, H.; Goldenberg, D. M.; **Hansen, H. J.**
CS Immunomedics, Inc., Morris Plains, NJ, USA
SO Journal of Nuclear Medicine, (May, 2000) Vol. 41, No. 5 Suppl., pp. 270P. print.
Meeting Info.: 47th Annual Meeting of the Society of Nuclear Medicine. St. Louis, Missouri, USA. June 03-07, 2000. Society of Nuclear Medicine.
CODEN: JNMEAQ. ISSN: 0161-5505.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 6 Jul 2000
Last Updated on STN: 7 Jan 2002

L13 ANSWER 20 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2000:294724 BIOSIS
DN PREV200000294724
TI Targeted delivery of tumor antigens to dendritic cell by an invariant chain-specific antibody, LL1.
AU **Leung, Shui-On** [Reprint author]; Nakagawa, T. Y.; Mao, L.; **Qu, Z.**; Goldman, L.; Rudensky, A. Y.; Goldenberg, D. M.; **Hansen, H. J.**
CS Garden State Cancer Ctr, Belleville, NJ, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) Vol. 41, pp. 877. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 6 Jul 2000
Last Updated on STN: 7 Jan 2002

L13 ANSWER 21 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2000:244976 BIOSIS
DN PREV200000244976
TI Rapid clearance and instability of humanized IgG1 antibody F(ab')2 fragments in vivo.

AU Sharkey, Robert M. [Reprint author]; **Qu, Z. Timothy**; Karacay, H.; **Leung, S.**; **Hansen, H.**; Goldenberg, D. M.
CS Garden State Cancer Ctr, Belleville, NJ, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 286-287. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Jun 2000
Last Updated on STN: 5 Jan 2002

L13 ANSWER 22 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2000:200957 BIOSIS
DN PREV200000200957
TI The use of bispecific fusion antibody for delivery of small molecules to tumors.
AU **Qu, Z. Timothy** [Reprint author]; **Hansen, H. J.**; Losman, M. J.; Eliassen, K. C.; Sharkey, R. M.; McBride, W. J.; Barbet, J.; Goldenberg, D. M.; **Leung, S. O.**
CS Garden State Cancer Ctr, Belleville, NJ, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 3. print.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 17 May 2000
Last Updated on STN: 5 Jan 2002

L13 ANSWER 23 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1999:211966 BIOSIS
DN PREV199900211966
TI Recombinant expression of ribonuclease of Rana pipien origin.
AU **Leung, S. O.** [Reprint author]; Wang, J. R.; **Qu, Z.**; Losman, M. J.; Goldenberg, D. M.; **Hansen, H. J.**
CS Immunomedics Inc., Morris Plains, NJ 07950, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 353-354. print.
Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research. Philadelphia, Pennsylvania, USA. April 10-14, 1999. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 May 1999
Last Updated on STN: 26 May 1999

L13 ANSWER 24 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1998:356210 BIOSIS
DN PREV199800356210
TI Carbohydrates engineered at antibody constant domains can be used for site-specific conjugation of drugs and chelates.
AU **Qu, Zhengxing**; Sharkey, Robert M.; **Hansen, Hans J.**; Shih, Lisa B.; Govindan, Serengulam V.; Shan, Jian; Goldenberg, David M.; **Leung, Shui-On** [Reprint author]

CS Immunomed., Morris Plains, NJ 07950, USA
SO Journal of Immunological Methods, (April 15, 1998) Vol. 213, No. 2, pp. 131-144. print.
CODEN: JIMMBG. ISSN: 0022-1759.
DT Article
LA English
ED Entered STN: 27 Aug 1998
Last Updated on STN: 27 Aug 1998
AB To improve the efficiency of site-specific conjugation of chelates and drugs to antibodies, and to minimize the incidence of immunoreactivity perturbation to the resultant immunoconjugates, Asn-linked oligosaccharide moieties were designed and engineered into the constant domains of a humanized anti-CD22 monoclonal antibody, hLL2. From 10 potential glycosylation mutants, two CH1 domain glycosylation sites, HCN1 and HCN5, were identified that were positioned favorably for glycosylation. The carbohydrate (CHO) chains attached at these sites were differentially processed so that HCN5-CHOs were physically larger than HCN1-CHOs. Although both the CH1-appended CHOs, and the LL2 Vkappa-appended CHOs conjugated efficiently with small chelates, the HCN5-CHOs, due to the structural and positional superiority, appear to be a better conjugation site for large drug complexes, such as 18 kDa doxorubicin (DOX)-dextran.

L13 ANSWER 25 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1998:203673 BIOSIS
DN PREV199800203673
TI Characterization of antibody mutants with a deleted CH2 domain and F(ab')2 carrying a human IgG3 hinge.
AU **Leung, S. O.** [Reprint author]; **Qu, Z.**; Losman, M. J.; Wang, J. R.; Sharkey, R. M.; Goldenberg, D. M.; **Hansen, H. J.**
CS Immunomedics Inc., Morris Plains, NJ 07950, USA
SO FASEB Journal, (March 20, 1998) Vol. 12, No. 5, pp. A914. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology 98, Part II. San Francisco, California, USA. April 18-22, 1998. Federation of American Societies for Experimental Biology.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 4 May 1998
Last Updated on STN: 4 May 1998

L13 ANSWER 26 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1998:196854 BIOSIS
DN PREV199800196854
TI Glycosylation improves the serum stability of antibody fragment of humanized LL2.
AU **Qu, Z.** [Reprint author]; Sharkey, R. M.; Shih, L. B.; **Hansen, H. J.**; Goldenberg, D. M.; **Leung, S. O.**
CS Immunomedics Inc., Morris Plains, NJ 07950, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 438. print.
Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research. New Orleans, Louisiana, USA. March 28-April 1, 1998. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 4 May 1998
Last Updated on STN: 4 May 1998

L13 ANSWER 27 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on

STN
AN 1998:194307 BIOSIS
DN PREV199800194307
TI Induction of apoptosis on B-lymphomas cells by two rapidly internalizing antibodies.
AU **Leung, S. O.** [Reprint author]; Wang, J. R.; Losman, M. J.; **Qu, Z.**; Goldenberg, D. M.; **Hansen, H. J.**
CS Immunomedics Inc., Morris Plains, NJ 07950, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1998) Vol. 39, pp. 63. print.
Meeting Info.: 89th Annual Meeting of the American Association for Cancer Research. New Orleans, Louisiana, USA. March 28-April 1, 1998. American Association for Cancer Research.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 4 May 1998
Last Updated on STN: 4 May 1998

L13 ANSWER 28 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1998:52483 BIOSIS
DN PREV199800052483
TI Generation of a high-producing clone of a humanized anti-B-cell lymphoma monoclonal antibody (hLL2).
AU Losman, Michele J.; **Hansen, Hans J.**; Dworak, Heather; Krishnan, Indira S.; **Qu, Zhengxing**; Shih, Lisa B.; Zeng, Li; Goldenberg, David M.; **Leung, Shui-On** [Reprint author]
CS Immunomedics Inc., 300 American Rd., Morris Plains, NJ 07950, USA
SO Cancer, (Dec. 15, 1997) Vol. 80, No. 12 SUPPL., pp. 2660-2666. print.
CODEN: CANCAR. ISSN: 0008-543X.
DT Article
LA English
ED Entered STN: 27 Jan 1998
Last Updated on STN: 27 Jan 1998
AB BACKGROUND. LL2 is a murine immunoglobulin (Ig)G2a-kappa anti-B-cell monoclonal antibody with proven targeting and therapeutic efficacy in the management of non-Hodgkin's lymphoma (NHL). The authors had previously generated a humanized LL2 (hLL2) that demonstrated binding properties identical to those of LL2. Nevertheless, the productivity of the cell line was insufficient for large-scale production of the antibody for clinical studies. Therefore, the authors chose an amplifiable system for the generation of hLL2. METHODS. The hLL2 sequences were ligated into the expression vector pdHL2, which has a dhfr amplifiable gene, and were incorporated into the SP2/0 cells by electroporation. A methotrexate (MTX) resistant clone producing hLL2 was identified. Stepwise increases in MTX concentrations, from 0.1 to 5 muM, and subcloning of the cells by limiting dilution were performed. RESULTS. By amplifying the dhfr and hLL2 genes with stepwise increases in the MTX concentration, the antibody production was enhanced from its original 1.4 to 70 +- 5 mg per liter of culture media. Subsequent subcloning further improved the productivity. Immunoreactivity of the antibody was conserved, as proven by enzyme-linked immunosorbent assay and cell-binding assays. By isoelectrofocusing, the isoelectric point (pI) of the antibody was measured at approximately 9.6. The productivity of the clone was not affected by culture conditions or storage of the cells in liquid nitrogen. CONCLUSIONS. By means of gene amplification, the authors have generated a high-producing hLL2-IgG clone suitable for production of the quantity of antibody necessary for clinical diagnostic and therapeutic trials of NHL patients.

L13 ANSWER 29 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1997:454720 BIOSIS

DN PREV199799753923
TI Structure determination of N-linked oligosaccharides engineered at the CH-1 domain in humanized LL2.
AU **Qu, Zhengxing**; Sharkey, Robert M.; **Hansen, Hans J.**; Goldenberg, David M.; **Leung, Shui-On** [Reprint author]
CS Immunomedics, Inc., 300 American Rd., Morris Plains, NJ 07950, USA
SO Glycobiology, (1997) Vol. 7, No. 6, pp. 803-809.
ISSN: 0959-6658.
DT Article
LA English
ED Entered STN: 27 Oct 1997
Last Updated on STN: 27 Oct 1997
AB Two humanized antibody mutants, hLL2HCN1 and hLL2HCN5, engineered with CH-1 domain-appended carbohydrates (CHOs) were generated to facilitate site-specific conjugation of radionuclides and anti-cancer drugs to antibodies. Such site-specific conjugation may minimize the incidence of immunoreactivity perturbation as is often observed with random conjugation. Since the compositions and structures of CHOs are important in determining the chemistry, efficiency, and extent of conjugation, the sequences of the CH-1-appended CHOs were determined by exoglycosidase digestions and fluorophore-assisted CHO electrophoresis (FACE). The CHO species attached at HCN1 and HCN5 sites in hLL2HCN1 and hLL2HCN5, respectively, were distinct from each other, heterogeneous, and extensively processed. All of these CHOs were core-fucosylated complex-type oligosaccharides and contained Gal (galactose) and GlcNAc (N-acetylglucosamine) residues in the outer branches. Some of the outer branches were composed of Gal-alpha-1-3Gal-beta-1-4GlcNAc structure, also known as alpha-galactosyl epitope. Most of the CHOs were sialylated. While all HCN1-CHOs were biantennary, the majority of HCN5-CHOs (gt 60%) were triantennary. The CH-1-appended CHOs have favorable structural characteristics suitable for site-specific conjugation. For efficient conjugation of large drug complexes, hLL2HCN5 is preferable to hLL2HCN1 because the attached CHO is larger in size and more remotely positioned from the V region. The effects of the alpha-galactosyl epitope found in these CHOs on the immunological properties of the immunoconjugates as efficient cancer diagnostics and therapeutics are being studied.

L13 ANSWER 30 OF 42 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 1996:257292 BIOSIS
DN PREV199698813421
TI Antibody glycoengineering for the generation of novel sites for site-specific conjugation.
AU **Qu, Z.** [Reprint author]; Sharkey, R. M.; **Hansen, H. J.** [Reprint author]; Goldenberg, D. M.; **Leung, S. O.** [Reprint author]
CS Immunomedics Inc., Morris Plains, NJ 07950, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 468.
Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research. Washington, D.C., USA. April 20-24, 1996.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 31 May 1996
Last Updated on STN: 31 May 1996

L13 ANSWER 31 OF 42 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 1999367269 EMBASE
TI The effects of domain deletion, glycosylation, and long IgG3 hinge on the biodistribution and serum stability properties of a humanized IgG1

immunoglobulin, hLL2, and its fragments.
AU **Leung S.-O.**; **Qu Z.**; **Hansen H.J.**; Shih L.B.; Wang J.; Losman M.J.; Goldenberg D.M.; Sharkey R.M.
CS S.-O. Leung, Department of Biology Research, Immunomedics, Inc., 300 American Road, Morris Plains, NJ 07950, United States
SO Clinical Cancer Research, (1999) Vol. 5, No. 10 SUPPL., pp. 3106s-3117s. Refs: 68
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Conference Article
FS 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 19991104
Last Updated on STN: 19991104
AB Antibody (Ab) fragments are preferred agents for imaging applications because of their rapid clearance from the blood, thereby providing high tumor:blood ratios within a few hours. Several preclinical studies have also suggested that Ab fragments might be preferred for therapeutic applications over an intact IgG. The purpose of this project was to develop engineered Ab fragments using a humanized anti-carcinoembryonic antigen and anti-CD22 Ab as the parent. Three types of variants were prepared: a ΔCH2 (deletion mutant missing the CH2), a γ3 F(ab')2 containing the human IgG3 hinge, and three glycosylated variants. The γ3 F(ab')2 and glycosylated variants were developed because of the potential for site-specific linkage to the Ab in its divalent or monovalent fragment. The γ3 F(ab')2 variant contains 10 cysteine residues that could be used for direct coupling using thiol chemistry, whereas the glycosylated variants have N-linked glycosylation sites engineered in the CH1 domain (two variants) as well as the VK domain (one variant). All of these variants were successfully prepared and shown to react with the target antigen. All Abs could be purified to a single peak by size-exclusion HPLC, but the ΔCH2 variant showed two distinct peaks, which were believed to be both the divalent and monovalent forms of this fragment. The two CH1 glycosylated variants showed differences in the extent of glycosylation. Modeling studies suggest that one variant would be better suited for site-specific coupling than the other because the carbohydrate chain is extended further away from the antigen-binding site. The Abs were radioiodinated to determine their pharmacokinetic behavior in mice. All of the humanized Ab divalent fragments cleared nearly 20 times faster from the blood than the murine parent F(ab')2 over a 24-h period. The glycosylated fragments showed some added stability compared to the other fragments over 4 h, but by 24 b, they had cleared to the same extent. Size-exclusion high- performance liquid chromatography of blood samples indicated that the humanized Ab fragments were quickly degraded in the blood. Thus, there is an inherent instability of the divalent fragments from these humanized IgG1 constructs that may affect their utility in imaging or therapy applications.

L13 ANSWER 32 OF 42 EMBASE
AN 1999367268 EMBASE
TI Generation and monitoring of cell lines producing humanized antibodies.
AU Losman M.J.; **Qu Z.**; Krishnan I.S.; Wang J.; **Hansen H.J.**; Goldenberg D.M.; **Leung S.-O.**
CS S.-O. Leung, Immunomedics, Inc., 300 American Road, Morris Plains, NJ 07950, United States
SO Clinical Cancer Research, (1999) Vol. 5, No. 10 SUPPL., pp. 3101s-3105s. Refs: 30
ISSN: 1078-0432 CODEN: CCREF4
CY United States

DT Journal; Conference Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
ED Entered STN: 19991112
Last Updated on STN: 19991112
AB Antibody humanization has eliminated or reduced the human antimouse antibody response associated with the administration of murine antibodies. We have successfully humanized three different antibodies: (a) hMN-3 (granulocyte targeting); (b) hMu-9 (colorectal cancer targeting); and (c) hWI2 (anti-idiotype to the anti-carcinoembryonic anti. gen antibody MN-14). All humanized antibodies demonstrated immunoreactivities comparable to their parent counterparts. Previously, we reported the generation of high productivity cell lines for hMN-14 and hLL2 using the amplifiable vector pdHL2. Through amplification, selection, and cloning procedures, cell lines capable of large scale production were established, and further enhancement of production was achieved by a fed-perfusion bioreactor process. Using a similar and improved approach, we have enhanced the production of the above- mentioned humanized antibodies by gene amplification induced by a stepwise increase in the concentration of methotrexate in the culture media. A reliable IgG determination method is essential to monitor amplification, especially at the final cloning stage, for the selection of the subclones with the highest productivity. We found that measurement of humanized IgG concentration in culture media supplemented with more than 1 μM methotrexate by a standard ELISA assay could be unreliable and misleading. Whereas the determination of antibody by adsorption/elution on protein A from a 100-ml culture is accurate and reproducible, the method is time-consuming, tedious, and labor intensive. We have recently developed a Western blot assay that enables us to monitor the productivity of the cultures. The assay is simple and sensitive, and it makes simultaneous determinations of relative antibody production from individual clones at the 96-well stage feasible. With this method, amplification, cloning, and adaptation to serum-free conditions of multiple cell lines can be monitored in an efficient manner.

L13 ANSWER 33 OF 42 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 1999367267 EMBASE
TI Humanization of Immu31, an α-fetoprotein-specific antibody.
AU **Qu Z.**; Losman M.J.; Eliassen K.C.; **Hansen H.J.**; Goldenberg D.M.; **Leung S.-O.**
CS S.-O. Leung, Immunomedics, Inc., 300 American Road, Morris Plains, NJ 07950, United States
SO Clinical Cancer Research, (1999) Vol. 5, No. 10 SUPPL., pp. 3095s-3100s. Refs: 36
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Conference Article
FS 022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
ED Entered STN: 19991112
Last Updated on STN: 19991112
AB Immu31 is a murine monoclonal antibody (Ab) specific for α-fetoprotein (AFP), a tumor-associated marker. The excellent tumor targeting ability of Immu31 has led to the development of a Immu31-based radioimmunodiagnostic agent, AFP-Scan, for hepatocellular carcinoma and other AFP-producing tumors. To enhance the capability of Immu31-based immunoconjugates being used in diagnostic and therapeutic procedures in humans, a humanized version of Immu31 (hImmu31) was constructed by grafting the complementarity determining regions (CDRs) of murine variable domains for the heavy (VH) and κ (Vκ) chain to the respective

human VH and Vκ framework regions (FRs). The cDNA encoding the VH and Vκ of Immu31 was cloned by reverse transcription-PCR from hybridoma cells, and a chimeric Immu31 (cImmu31) composed of murine V and human C domains was constructed. Competitive ELISA assays showed identical AFP binding activity between the chimeric and murine Abs, confirming the authenticity of the cloned V genes. Based on sequence homology, the EU FR1, FR2, and FR3 and the NEWM FR4 were selected as the scaffold for grafting VH CDRs and REI FRs for Vκ CDRs of Immu31. The amino acid residues in murine FRs that are considered to be in contact with the CDRs of the Ab were maintained in the humanized version, hImmu31, thus constructed and expressed, showed comparable immunoreactivity in a competitive binding ELISA assay to that of murine Immu31 and cImmu31. High- level production was achieved by expressing hImmu31 in a dhfr-based amplifiable system, and the productivity has exceeded 100 mg/liter in terminal cultures.

L13 ANSWER 34 OF 42 EMBASE
AN 1998241744 EMBASE
TI Carbohydrates engineered at antibody constant domains can be used for site-specific conjugation of drugs and chelates.
AU **Qu Z.**; Sharkey R.M.; **Hansen H.J.**; Shih L.B.; Govindan S.V.; Shen J.; Goldenberg D.M.; **Leung S.-O.**
CS S.-O. Leung, Immunomedics, Morris Plains, NJ 07950, United States. sleung@ibm.net
SO Journal of Immunological Methods, (1998) Vol. 213, No. 2, pp. 131-144.
Refs: 42
ISSN: 0022-1759 CODEN: JIMMBG
PUI S 0022-1759(97)00192-0
CY Netherlands
DT Journal; Article
FS 022 Human Genetics
026 Immunology, Serology and Transplantation
LA English
SL English
ED Entered STN: 19980820
Last Updated on STN: 19980820
AB To improve the efficiency of site-specific conjugation of chelates and drags to antibodies, and to minimize the incidence of immunoreactivity perturbation to the resultant immunoconjugates, Ash-linked oligosaccharide moieties were designed and engineered into the constant domains of a humanized anti-CD22 monoclonal antibody, hLL2. From 10 potential glycosylation mutants, two CH1 domain glycosylation sites, HCN1 and HCN5, were identified that were positioned favorably for glycosylation. The carbohydrate (CHO) chains attached at these sites were differentially processed so that HCN5-CHOs were physically larger than HCN1-CHOs. Although both the CH1-appended CHOs, and the LL2 V(κ),-appended CHOs conjugated efficiently with small chelates, the HCN5-CHOs, due to the structural and positional superiority, appear to be a better conjugation site for large drug complexes, such as 18 kDa doxorubicin (DOX)-dextran.

L13 ANSWER 35 OF 42 EMBASE
AN 1998004768 EMBASE
TI Generation of a high-producing clone of a humanized anti-B-cell lymphoma monoclonal antibody (hLL2).
AU Losman M.J.; **Hansen H.J.**; Dworak H.; Krishnan I.S.; **Qu Z.**; Shih L.B.; Zeng L.; Goldenberg D.M.; **Leung S.-O.**
CS Dr. S.-O. Leung, Immunomedics Inc., 300 American Road, Morris Plains, NJ 07950, United States
SO Cancer, (1997) Vol. 80, No. 12 SUPPL., pp. 2660-2666.
Refs: 36
ISSN: 0008-543X CODEN: CANCAR
CY United States

DT Journal; Conference Article
FS 016 Cancer
026 Immunology, Serology and Transplantation
LA English
SL English
ED Entered STN: 19980120
Last Updated on STN: 19980120
AB BACKGROUND. LL2 is a murine immunoglobulin (Ig)G2a-kappa anti-B-cell monoclonal antibody with proven targeting and therapeutic efficacy in the management of non-Hodgkin's lymphoma (NHL). The authors had previously generated a humanized LL2 (hLL2) that demonstrated binding properties identical to those of LL2. Nevertheless, the productivity of the cell line was insufficient for large-scale production of the antibody for clinical studies. Therefore, the authors chose an amplifiable system for the generation of hLL2. METHODS. The hLL2 sequences were ligated into the expression vector pdHL2, which has a dhfr amplifiable gene, and were incorporated into the SP2/0 cells by electroporation. A methotrexate (MTX) resistant clone producing hLL2 was identified. Stepwise increases in MTX concentrations, from 0.1 to 5 μM, and subcloning of the cells by limiting dilution were performed. RESULTS. By amplifying the dhfr and hLL2 genes with stepwise increases in the MTX concentration, the antibody production was enhanced from its original 14 to 70 ± 5 mg per liter of culture media. Subsequent subcloning further improved the productivity. Immunoreactivity of the antibody was conserved, as proven by enzyme-linked immunosorbent assay and cell-binding assays. By isoelectrofocusing, the isoelectric point (pI) of the antibody was measured at approximately 9.6. The productivity of the clone was not affected by culture conditions or storage of the cells in liquid nitrogen. CONCLUSIONS. By means of gene amplification, the authors have generated a high-producing hLL2-IgG clone suitable for production of the quantity of antibody necessary for clinical diagnostic and therapeutic trials of NHL patients.

L13 ANSWER 36 OF 42 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN
AN 97276914 EMBASE
DN 1997276914
TI Structure determination of N-linked oligosaccharides engineered at the CH1 domain of humanized LL2.
AU **Qu Z.**; Sharkey R.M.; **Hansen H.J.**; Goldenberg D.M.; **Leung S.**
CS S. Leung, Immunomedics Inc., 300 American Road, Morris Plains, NJ 07950, United States
SO Glycobiology, (1997) Vol. 7, No. 6, pp. 803-809.
Refs: 31
ISSN: 0959-6658 CODEN: GLYCE3
CY United Kingdom
DT Journal; Article
FS 016 Cancer
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 970925
Last Updated on STN: 970925
AB Two humanized antibody mutants, hLL2HCN1 and hLL2HCN5, engineered with CH1 domain-appended carbohydrates (CHOs) were generated to facilitate site-specific conjugation of radionuclides and anti-cancer drugs to antibodies. Such site-specific conjugation may minimize the incidence of immunoreactivity perturbation as is often observed with random conjugation. Since the compositions and structures of CHOs are important in determining the chemistry, efficiency, and extent of conjugation, the sequences of the CH1-appended CHOs were determined by exoglycosidase digestions and fluorophore-assisted CHO electrophoresis (FACE). The CHO species attached at HCN1 and HCN5 sites in hLL2HCN1 and hLL2HCN5,

respectively, were distinct from each other, heterogeneous, and extensively processed. All of these CHOs were corefucosylated complex-type oligosaccharides and contained Gal (galactose) and GlcNAc (N-acetylglucosamine) residues in the outer branches. Some of the outer branches were composed of Galα1-3Galβ1-4GlcNAc structure, also known as α-galactosyl epitope. Most of the CHOs were sialylated. While all HCN1-CHOs were biantennary, the majority of HCN5-CHOs (>60%) were triantennary. The CH1-appended CHOs have favorable structural characteristics suitable for site-specific conjugation. For efficient conjugation of large drug complexes, hLL2HCN5 is preferable to hLL2HCN1 because the attached CHO is larger in size and more remotely positioned from the V region. The effects of the α-galactosyl epitope found in these CHOs on the immunological properties of the immunoconjugates as efficient cancer diagnostics and therapeutics are being studied.

L13 ANSWER 37 OF 42 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2004-042533 [04] WPIDS
CR 1994-083215 [10]; 1997-051905 [05]; 1998-130831 [12]; 2000-160561 [14]; 2000-423227 [36]; 2003-167089 [16]
DNC C2004-017457
TI New compound, useful for preparing a composition for diagnosing or treating tumor or infections caused by fungus, virus, parasite, bacterium, protozoan or mycoplasm.
DC B04 D16 K08
IN GOLDENBERG, D M; **HANSEN, H**; **LEUNG, S**; MCBRIDE, W J; **QU, Z**; **HANSEN, H J**
PA (IMMU-N) IMMUNOMEDICS INC; (MCCA-I) MCCALL J D
CYC 104
PI WO 2003097105 A1 20031127 (200404)* EN 119
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
AU 2003227939 A1 20031202 (200442)
EP 1506018 A1 20050216 (200513) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
BR 2003010088 A 20050405 (200524)
KR 2004111640 A 20041231 (200528)
MX 2004011422 A1 20050301 (200568)
ADT WO 2003097105 A1 WO 2003-GB2110 20030516; AU 2003227939 A1 AU 2003-227939 20030516; EP 1506018 A1 EP 2003-725404 20030516, WO 2003-GB2110 20030516; BR 2003010088 A BR 2003-10088 20030516, WO 2003-GB2110 20030516; KR 2004111640 A KR 2004-718606 20041117; MX 2004011422 A1 WO 2003-GB2110 20030516, MX 2004-11422 20041117
FDT AU 2003227939 A1 Based on WO 2003097105; EP 1506018 A1 Based on WO 2003097105; BR 2003010088 A Based on WO 2003097105; MX 2004011422 A1 Based on WO 2003097105
PRAI US 2002-150654 20020517
AB WO2003097105 A UPAB: 20051024
NOVELTY - A compound, useful for preparing a composition for diagnosing or treating tumor or infections caused by fungus, virus, parasite, bacterium, protozoan or mycoplasm, comprising the formula (I), is new.
DETAILED DESCRIPTION - A compound, useful for preparing a composition for diagnosing or treating tumor or infections caused by fungus, virus, parasite, bacterium, protozoan or mycoplasm, comprising the formula (I):
X-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-Lys(Y)-NH2 (I)
The compound includes a hard acid cation chelator at X or Y, and a soft acid cation chelator at remaining X or Y.
INDEPENDENT CLAIMS are also included for:
(1) a targetable construct;

(2) a method of diagnosing or treating a disease or condition that may lead to a disease;
(3) a method for detecting or treating target cells, tissues or pathogens in a mammal;
(4) a method of treating or identifying diseased tissues in a subject;
(5) a kit for treating or identifying diseased tissues in a subject;
(6) a method for imaging normal tissue in a mammal;
(7) a method of intra-operatively identifying diseased tissues in a subject;
(8) a method for the endoscopic identification of diseased tissues in a subject; and
(9) a method for the intravascular identification of diseased tissues in a subject.
ACTIVITY - Cytostatic; Virucide; Antifungal; Antiparasitic; Antibacterial; Protozoacide.
No biological data given.
MECHANISM OF ACTION - Gene therapy.
USE - The compound is useful for preparing a composition for diagnosing or treating tumor or infections caused by fungus, virus, parasite, bacterium, protozoan or mycoplasm (claimed).
Dwg.0/7

L13 ANSWER 38 OF 42 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-767381 [72] WPIDS
CR 1999-045130 [04]; 2001-041267 [05]; 2001-122704 [13]; 2002-351262 [38]; 2005-010089 [01]
DNN N2003-614702 DNC C2003-210871
TI New humanized, human or chimeric anti-CD74 antibody or fragment, useful for diagnosing or treating a CD74 expressing malignancy, an immune dysregulation disease, an autoimmune disease or graft versus host disease.
DC B04 D16 S03
IN GOLDENBERG, D M; **HANSEN, H**; **LEUNG, S**; **QU, Z**; **HANSEN, H J**
PA (IMMU-N) IMMUNOMEDICS INC; (MCCA-I) MCCALL J D
CYC 103
PI WO 2003074567 A2 20030912 (200372)* EN 91
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
AU 2003215732 A1 20030916 (200430)
US 2004115193 A1 20040617 (200440)
EP 1483294 A2 20041208 (200480) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
KR 2004089695 A 20041021 (200514)
CN 1649902 A 20050803 (200578)
ADT WO 2003074567 A2 WO 2003-GB890 20030303; AU 2003215732 A1 AU 2003-215732 20030303; US 2004115193 A1 Provisional US 2002-360259P 20020301, US 2003-377122 20030303; EP 1483294 A2 EP 2003-743421 20030303, WO 2003-GB890 20030303; KR 2004089695 A KR 2004-713665 20040901; CN 1649902 A CN 2003-809863 20030303, WO 2003-GB890 20030303
FDT AU 2003215732 A1 Based on WO 2003074567; EP 1483294 A2 Based on WO 2003074567
PRAI US 2002-360259P 20020301; US 2003-377122 20030303
AB WO2003074567 A UPAB: 20051205
NOVELTY - A humanized, human or chimeric anti-CD74 antibody or fragment, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a humanized anti-CD74 monoclonal antibody (mAb) or its fragment comprising light and heavy chain variable regions having complementarity-determining regions (CDRs) of murine anti-CD74 (mLL1) and the framework (FR) regions of a human antibody, where the light chain variable region of the humanized mAb comprises CDRs of a light chain variable region of a murine anti-CD74 mAb, that comprises:

(a) CDR1 with amino acid sequence S1, (S1) RSSQSLVHRNGNTYLH;

(b) CDR2 comprising amino acid sequence S2, (S2) TVSNRFS;

(c) CDR3 comprising amino acid sequence S3, (S3) SQSSHVPPT; and

(d) where the heavy chain variable region of the humanized mAb comprises CDRs of a heavy chain variable region of the murine anti-CD74 mAb, that comprises CDR1 comprising amino acid sequence S4, (S4) NYGVN;

(e) CDR2 comprising amino acid sequence S5, (S5) WINPNTGEPTFDDDFKG; and

(f) CDR3 comprising amino acid sequence S6, (S6) SRGKNEAWFAY;

(2) a murine anti-CD74 mAb or fragment, comprising CDRs of a light chain variable region of a murine anti-CD74 mAb, that comprises CDR1 comprising amino acid sequence S1, CDR2 comprising amino acid sequence S2, and CDR3 comprising amino acid sequence S3, or CDRs of a heavy chain variable region of a murine anti-CD74 mAb, that comprises CDR1 comprising amino acid sequence S4, CDR2 comprising amino acid sequence S5, and CDR3 comprising amino acid sequence S6;

(3) an antibody fusion protein comprising four or more Fvs, or Fab's of the mAbs or fragments cited above, and/or one or more Fvs or Fab's from antibodies specific for a tumor cell marker that is not a CD74 antigen;

(4) an immunoconjugate conjugate, comprising an antibody component comprising at least one mAb or fragment or antibody fusion protein cited above, that binds to CD74, where the antibody component is linked to a diagnostic or therapeutic agent;

(5) treating a disease or disorder comprising administering to a subject a therapeutic composition comprising a pharmaceutically acceptable carrier and at least one mAb or fragment or antibody fusion protein or an immunoconjugate cited above;

(6) treating a malignancy, comprising administering to a subject with a CD74 antigen positive malignancy other than lymphoma or leukemia, a therapeutic composition comprising a carrier and at least one mAb or fragment or an antibody fusion protein cited above;

(7) treating a subject with at least one disease diagnosed as an immune dysregulation disease and autoimmune disease, comprising administering to the subject a therapeutic composition comprising a carrier and at least one mAb or fragment or an antibody fusion protein cited above;

(8) treating or diagnosing one of the diseases selected from the group consisting of lymphoma, leukemia, other CD-74 expressing malignancies, immune dysregulation disease, autoimmune disease and their combination, comprising administering a therapeutic composition comprising a carrier and at least one mAb or fragment or an antibody fusion protein cited above, where at least one therapeutic agent is linked to the mAb or fragment or the Fvs or Fab's of the antibody fusion protein by chemical conjugation or by genetic fusion;

(9) a vaccine comprising covalent linked of mAbs or fragments cited above to class-I or class-II MHC antigenic peptides forming an antibody conjugate, where the vaccine is used to treat patients with cancer or infectious disease;

(10) a bispecific or multispecific antibody, where the mAbs or fragments or antibody fusion proteins cited above, are linked to an antibody or antibody fragment specific for a cancer or inflammatory cell marker substance, an epitope on the surface of a infectious disease organism, or a noxious substance in the blood or other body fluid;

(11) a DNA sequence comprising a nucleic acid encoding a mAb or fragment selected from:

(a) an anti-CD74mAb or fragment cited above;

(b) an immunoconjugate of (4);

(c) an antibody fusion protein or fragment comprising at least two of

the anti-CD74 mAbs or fragments cited above;
(d) an antibody fusion protein or fragment of (3);
(e) a vaccine of (9); and
(f) a bispecific or multispecific antibody of (10);
(12) an expression vector comprising the DNA sequence of (11);
(13) a host cell comprising the DNA sequence of (11); and
(14) expression of an anti-CD74mAb or fragment or antibody fusion protein or fragment, comprising transfecting a host cell with a DNA sequence of (11), and culturing the cell secreting the anti-CD74 mAb or antibody fusion protein or their fragments.
ACTIVITY - Cytostatic; Immunosuppressive; Immunomodulator.
No biological data given.
MECHANISM OF ACTION - CD74-Antagonist.
USE - The naked anti-CD74 antibody or a naked antibody fusion protein or fragment, or a therapeutic or diagnostic conjugate comprising an anti-CD74 antibody is useful for diagnosing or treating a disorder or a disease that is a CD74 expressing malignancy (solid tumor, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, another B-cell malignancy and a T-cell malignancy), an immune dysregulation disease, an autoimmune disease, organ graft rejection, and graft versus host disease. The solid tumor is melanoma, carcinoma and sarcoma. The carcinoma is a renal carcinoma, lung carcinoma, intestinal carcinoma, stomach carcinoma and melanoma. The B-cell malignancy is of non-Hodgkin's lymphoma, Hodgkin's lymphoma, indolent forms of B-cell lymphomas, aggressive forms of B-cell lymphomas, chronic lymphatic leukemias, acute lymphatic leukemias, and multiple myeloma (all claimed).
Dwg.0/10

L13 ANSWER 39 OF 42 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2003-167089 [16] WPIDS
CR 1994-083215 [10]; 1997-051905 [05]; 1998-130831 [12]; 2000-160561 [14]; 2000-423227 [36]; 2004-042533 [04]
DNN N2003-132137 DNC C2003-043271
TI Novel multivalent, multispecific antibody for detecting/treating tumors expressing colon specific antigen-p mucin in mammal, comprises antigen and hapten binding sites.
DC B04 B05 C03 C06 D16 E23 K08 S03
IN GOLDENBERG, D M; GRIFFITHS, G L; **HANSEN, H J**; **LEUNG, S**; MCBRIDE, W J; **QU, Z**
PA (IMMU-N) IMMUNOMEDICS INC
CYC 101
PI WO 2002082041 A2 20021017 (200316)* EN 202
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
EP 1372718 A2 20040102 (200409) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
AU 2002256025 A1 20021021 (200433)
JP 2005503768 W 20050210 (200511) 330
US 6962702 B2 20051108 (200573)
ADT WO 2002082041 A2 WO 2002-US10235 20020403; EP 1372718 A2 EP 2002-725464 20020403, WO 2002-US10235 20020403; AU 2002256025 A1 AU 2002-256025 20020403; JP 2005503768 W JP 2002-579763 20020403, WO 2002-US10235 20020403; US 6962702 B2 Provisional US 1998-90142P 19980622, Provisional US 1998-104156P 19981014, CIP of US 1999-337756 19990622, US 2001-823746 20010403
FDT EP 1372718 A2 Based on WO 2002082041; AU 2002256025 A1 Based on WO 2002082041; JP 2005503768 W Based on WO 2002082041
PRAI US 2001-823746 20010403; US 1998-90142P 19980622;

US 1998-104156P 19981014; US 1999-337756 19990622

AB WO 200282041 A UPAB: 20051114

NOVELTY - A multivalent, multispecific antibody (I) or its fragment comprising one more antigen binding sites having affinity towards colon specific antigen-p mucin (CSAp) target antigen and one or more hapten binding sites having affinity towards hapten molecules, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a monoclonal antibody (MAb) (II) or its fragment that binds to CSAp antigen;

(2) a complementarity determining region (CDR)-grafted humanized heavy or light chain (HC or LC) comprising CDRs of a murine anti-CSAp MAb and the framework region of the heavy chain variable region of a human antibody, and the heavy chain constant region of a human antibody, where the CDRs of the heavy chain variable region of the humanized anti-CSAp MAb comprises CDR1 comprising an amino acid sequence of Glu-Tyr-Val-Ile-Thr or Arg-Ser-Ser-Gln-Ser-Ile-Val-His-Ser-Asn-Gly-Asn-Thr-Tyr-Leu-Glu, CDR2 comprising an amino acid sequence of Glu-Ile-Tyr-Pro-Gly-Ser-Gly-Ser-Thr-Ser-Tyr-Asn-Glu-Lys-Phe-Lys or Lys-Val-Ser-Asn-Arg-Phe-Ser, and CDR3 comprising an amino acid sequence of EDL or Phe-Gln-Gly-Ser-Arg-Val-Pro-Tyr-Thr;

(3) an antibody fusion protein (III) or its fragment comprising at least two anti-CSAp MAbs or its fragment or (I), and second MAb or its fragment other than (I);

(4) a diagnostic/detection or therapeutic immunoconjugate (IV) comprising (I), (II) and (III), where the antibody component is bound to at least one diagnostic/detection agent or at least one therapeutic agent;

(5) a DNA sequence (V) comprising a nucleic acid encoding (I) and (II), where the MAb is selected from CEA, EGP-1, EGP-2, MUC-1,MUC-2, MUC-3, MUC-4, PAM-4, KC4, TAG-72, EGFR, HER2/neu, BrE3, LeY, A3, KS-1, CD40, VEGF, antibody, and the antibody A33, or their combination;

(6) an expression vector (VI) comprising (V);

(7) a host cell (VII) comprising (V);

(8) a targetable conjugate (VIII) selected from DOTA-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-NH2, DOTA-Phe-Lys(HSG)-Tyr-Lys(HSG)-NH2, Ac-Lys(HSG)-D-Tyr-Lys(HSG)-Lys(Tscg-Cys)-NH2, a compound of formula (F1) or (F2).

(9) treating (M1) a cancer cell by administering a composition comprising a naked anti-CSAp MAb or its fragment, naked antibody fusion protein or fragment of (I) and (II), formulating the mixture in a suitable excipient;

(10) diagnosing or detecting (M2) a malignancy in a subject by performing an in vitro diagnosis assay on a specimen from the subject with a composition comprising a naked anti-CSAp MAb or its fragment, naked antibody fusion protein or fragment of (I) and (II);

(11) treating or identifying (M3) diseased tissues in a subject by administering to the subject a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate, where the one arm that specifically binds a targeted tissue is Mu-9 antibody; optionally, administering a clearing composition, and allowing the composition to clear non-localized antibodies or antibody fragments from circulation; administering a first targetable conjugate which has a carrier portion which comprises or bears at least one epitope recognizable by at least one other arm of the bi-specific antibody or antibody fragment, and one or more conjugated therapeutic or diagnostic agents; and

(12) a kit useful for treating or identifying diseased tissues in a subject.

ACTIVITY - Cytostatic; Antitumor.

MECHANISM OF ACTION - Inhibitor of angiogenesis; Antibody therapy.

Therapy of a patient with 90Y-labeled humanized Mu-9 antibody was as follows: A 62-year-old man, with a history of Dukes' colon rectal carcinoma (CEA) that was resected 3 years earlier, at which time radiation therapy followed by 5-fluorouracil/folinic acid chemotherapy were given, began showing a rise in his plasma CEA titer over the last 6 months, reaching a level of 30 ng/ml. It was found, by computed tomography, that

there were two metastasis present in the liver, one being 3 cm in diameter in his right lobe, and the other being somewhat smaller in the left lobe. The patient was then given a dose of 25 mCi 90Y conjugated to the humanized Mu-9 antibody, given at a protein dose of 50 mg by intravenous infusion over a period of 2 hours. This therapy was then repeated one month later. The patients had a drop of his white blood cells and platelets, measured 2-4 weeks after the last therapy infusion, but recuperated at the 8-week post-therapy evaluation. The computed tomography findings at 3 months post-therapy revealed a 40% shrinkage of the major tumor metastasis of the right liver lobe, and a lesser reduction in the left-lobe tumor. At this time, the patient's blood CEA dropped to 15 ng/ml. At the 6-month follow-up, this tumor lesions had been reduced by about 70%, his plasma CEA was at 8 ng/ml, and his general condition was fine, with no apparent toxicity or adverse events related to the therapy.

USE - (I) is useful for screening a targetable conjugate. (IV) is useful for detecting close-range lesion. (I) and (IV) are useful for delivering a diagnostic/detection or therapeutic agent, or their combination, to a target. (I), (II) and (III) are useful for treating malignancy in a subject. (III), (IV) and fragments of (I) and (II) are useful for diagnosing or detecting malignancy in a subject. (I) and (VIII) are useful for detecting or treating tumors expressing CSAp in a mammal, for imaging malignant tissue or normal tissue or cells in a mammal expressing CSAp, where the normal tissue is from ovary, thymus, parathyroid or spleen, for intraoperatively identifying/disclosing the diseased tissues expressing CSAp in a subject, and for endoscopic identification of diseased tissues expressing CSAp. (I) and (VIII) are also useful for intravascular identification of diseased tissues expressing CSAp, for detecting lesions during an endoscopic, laparoscopic, intravascular catheter or surgical procedure, and for detecting and treating target cells, tissues or pathogens in a mammal. M2 is useful for diagnosing or detecting a malignancy in a subject, where the malignancy is carcinoma, gastrointestinal cancer, colorectal or pancreatic cancer or ovarian cancer, the subject is human or a domestic pet (all claimed). Dwg.0/12

L13 ANSWER 40 OF 42 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2000-160561 [14] WPIDS
CR 1994-083215 [10]; 1997-051905 [05]; 1998-130831 [12]; 2000-423227 [36]; 2003-167089 [16]; 2004-042533 [04]
DNC C2000-050075
TI Bi-specific antibodies that bind specific target tissue and targeted conjugates.
DC B04 D16 P14
IN GRIFFITHS, G L; **HANSEN, H J**; **LEUNG, S**; MCBRIDE, W J; **QU, Z**; GOLDENBERG, D M; NOREN, C; **HANSEN, H**; GOVINDAN, S
PA (IMMU-N) IMMUNOMEDICS INC; (GRIF-I) GRIFFITHS G L; (HANS-I) HANSEN H J; (LEUN-I) LEUNG S; (MCBR-I) MCBRIDE W J; (QUZZ-I) QU Z
CYC 109
PI WO 9966951 A2 19991229 (200014)* EN 76
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9945792 A 20000110 (200025)
EP 1089766 A2 20010411 (200121) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6228362 B1 20010508 (200128)
US 2002006379 A1 20020117 (200212)
JP 2002518460 W 20020625 (200243) 98
AU 760854 B 20030522 (200338)
US 2003198595 A1 20031023 (200370)
US 2005002945 A1 20050106 (200504)

US 2005169926 A1 20050804 (200552)
WO 2005077071 A2 20050825 (200556)# EN
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

ADT WO 9966951 A2 WO 1999-US13879 19990622; AU 9945792 A AU 1999-45792 19990622; EP 1089766 A2 EP 1999-928808 19990622, WO 1999-US13879 19990622; US 6228362 B1 Div ex US 1992-933982 19920821, CIP of US 1995-456393 19950601, CIP of US 1995-486166 19950607, CIP of US 1996-687626 19960726, Provisional US 1998-90142P 19980622, US 1998-205243 19981204; US 2002006379 A1 Provisional US 1998-90142P 19980622, Provisional US 1998-104156P 19981014, CIP of US 1999-337756 19990622, US 2001-823746 20010403; JP 2002518460 W WO 1999-US13879 19990622, JP 2000-555637 19990622; AU 760854 B AU 1999-45792 19990622; US 2003198595 A1 Provisional US 1998-90142P 19980622, Provisional US 1998-104156P 19981014, CIP of US 1999-382186 19990823, CIP of US 2001-823746 20010403, US 2002-150654 20020517; US 2005002945 A1 Provisional US 1998-90142P 19980622, Provisional US 1998-104156P 19981014, CIP of US 1999-337756 19990622, CIP of US 1999-382186 19990823, CIP of US 2001-823746 20010403, CIP of US 2002-150654 20020517, US 2004-776470 20040211; US 2005169926 A1 Provisional US 1998-90142P 19980622, Provisional US 1998-104156P 19981014, CIP of US 1999-337756 19990622, CIP of US 2001-823746 20010403, Div ex US 2002-116116 20020405, US 2005-70697 20050303; WO 2005077071 A2 WO 2005-US4177 20050211

FDT AU 9945792 A Based on WO 9966951; EP 1089766 A2 Based on WO 9966951; US 6228362 B1 Div ex US 525338, CIP of US 5698405, CIP of US 846741; JP 2002518460 W Based on WO 9966951; AU 760854 B Previous Publ. AU 9945792, Based on WO 9966951

PRAI US 1998-104156P 19981014; US 1998-90142P 19980622;
US 1992-933982 19920821; US 1995-456393 19950601;
US 1995-486166 19950607; US 1996-687626 19960726;
US 1998-205243 19981204; US 1999-337756 19990622;
US 2001-823746 20010403; US 1999-382186 19990823;
US 2002-150654 20020517; US 2004-776470 20040211;
US 2002-116116 20020405; US 2005-70697 20050303;
WO 2005-US4177 20050211

AB WO 9966951 A UPAB: 20050902

NOVELTY - A method of treating or identifying diseased tissues in a patient comprising administering a bi-specific antibody (or fragment) having at at least 1 arm (A) that specifically binds a targeted tissue and at least 1 arm (B) that specifically binds a targetable conjugate, is new.

DETAILED DESCRIPTION - A method of treating or identifying diseased tissues in a patient comprises:

(a) administering a bi-specific antibody (or fragment) comprising (A) and (B);

(b) administering to the patient a clearing composition, and allowing the composition to clear non-localized antibodies or antibody fragments from circulation (optional);

(c) administering a first targetable conjugate, which consists of a carrier portion comprising or bearing at least 1 epitope recognized by (B), and at least 1 conjugated therapeutic or diagnostic agent or enzyme; and

(d) administering (when the targetable conjugate comprises an enzyme):

(i) a prodrug;

(ii) a drug which is capable of being detoxified in the patient to form an intermediate of lower toxicity, when the enzyme is capable of reconverting the detoxified intermediate to a toxic form;

(iii) a prodrug which is activated in the patient through natural

processes and is subject to detoxification by conversion to an intermediate of lower toxicity, when the enzyme is capable of reconverting the detoxified intermediate to a toxic form, and therefore, of increasing the toxicity of the drug at the target site; or

(iv) a second targetable conjugate which consists of a carrier portion which comprises or bears at least 1 epitope recognizable by (B), and a prodrug.

INDEPENDENT CLAIMS are also included for the following:

(1) the bi-specific antibody or antibody fragment used in the above method;

(2) a kit useful for treating or identifying diseased tissues;

(3) a recombinant DNA construct comprising an expression cassette capable of producing in a host cell a bi-specific antibody as in (1);

(4) a set of expression cassettes capable of producing a bi-specific antibody (or fragment) as in (1);

(5) a method of preparing the bi-specific antibody; and

(6) methods of preparing a bi-specific fusion protein having at least 1 arm that specifically binds a targeted tissue and at least 1 other arm that specifically binds a targetable conjugate.

ACTIVITY - None given.

MECHANISM OF ACTION - None given.

USE - The methods and bi-specific antibodies and fusion proteins are useful for pre-targeting methods of diagnosis and therapy.

ADVANTAGE - It is advantageous to raise bi-specific antibodies against a targetable conjugate that is capable of carrying at least 1 diagnostic or therapeutic agent. The characteristics of the chelator, metal chelate complex, therapeutic agent or diagnostic agent can be varied to accommodate differing applications without raising new bi-specific antibodies for each new application. The targetable conjugate is selected to elicit sufficient immune responses and also for rapid in vivo clearance when used within the bi-specific antibody targeting method.

Dwg.0/5

L13 ANSWER 41 OF 42 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1999-337699 [28] WPIDS
DNN N1999-253077 DNC C1999-099303
TI Glycosylated antibodies with reactive ketone group at glycosylation sites.
DC B04 D16 S03
IN **HANSEN, H**; **LEUNG, S**; MCBRIDE, W J; **QU, Z**
PA (IMMU-N) IMMUNOMEDICS INC; (HANS-I) HANSEN H; (LEUN-I) LEUNG S; (MCBR-I) MCBRIDE W J; (QUZZ-I) QU Z
CYC 83
PI WO 9924472 A2 19990520 (199928)* EN 31
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9913729 A 19990531 (199941)
EP 1028978 A2 20000823 (200041) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
JP 2001522864 W 20011120 (200204) 36
US 2002193572 A1 20021219 (200303)
AU 757174 B 20030206 (200324)
US 6953675 B2 20051011 (200567)
ADT WO 9924472 A2 WO 1998-US23238 19981106; AU 9913729 A AU 1999-13729 19981106; EP 1028978 A2 EP 1998-957482 19981106, WO 1998-US23238 19981106; JP 2001522864 W WO 1998-US23238 19981106, JP 2000-520480 19981106; US 2002193572 A1 Provisional US 1997-64386P 19971106, US 1998-185607 19981104; AU 757174 B AU 1999-13729 19981106; US 6953675 B2 Provisional US 1997-64386P 19971106, US 1998-185607 19981104
FDT AU 9913729 A Based on WO 9924472; EP 1028978 A2 Based on WO 9924472; JP 2001522864 W Based on WO 9924472; AU 757174 B Previous Publ. AU 9913729,

Based on WO 9924472

PRAI US 1997-64386P 19971106; US 1998-185607 19981104

AB WO 9924472 A UPAB: 19990719

NOVELTY - Preparation of a glycosylated antibody (gAb), having a reactive ketone group on a glycosylation site is new.

DETAILED DESCRIPTION - Preparation of a glycosylated antibody (gAb), having a reactive ketone group on a glycosylation site comprises growing a cell, transfected with a vector encoding an antibody (Ab) with at least one glycosylation site, in a culture medium containing a ketone derivative (I) of a sugar or sugar precursor.

INDEPENDENT CLAIMS are also included for the following:

(a) production of fragments of gAb;

(b) production of immunoconjugates from gAb or its fragments; and

(c) gAb or its antigen-binding fragments, and immunoconjugates prepared from them.

ACTIVITY - Anticancer; antibacterial; antiviral; antiparasitic.

MECHANISM OF ACTION - None given.

USE - gAb, or its fragments, are used to produce immunoconjugates for in vivo delivery of active agents, particularly diagnostic and therapeutic agents, to a target site. Typical applications are diagnosis and treatment of cancer and infections (bacterial, viral or parasitic).

ADVANTAGE - Immunoconjugates are formed by attaching active agents to specific sites in Ab, without interferring with the binding specificity.

Dwg.0/0

L13 ANSWER 42 OF 42 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

AN 1997-479995 [44] WPIDS

CR 1998-447170 [38]

DNC C1997-152443

TI Monoclonal antibody engineered to contain glycosylation site - in non-Fc constant heavy or light chain region, useful to diagnose or treat B cell malignancies, e.g. non-Hodgkins lymphoma.

DC B04 D16

IN **HANSEN, H**; **LEUNG, S**; **QU, Z**; **HANSEN, H J**

PA (IMMU-N) IMMUNOMEDICS INC; (HANS-I) HANSEN H; (LEUN-I) LEUNG S; (QUZZ-I) QU Z

CYC 77

PI WO 9734632 A1 19970925 (199744)* EN 88

RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU

AU 9725318 A 19971010 (199806)

EP 888125 A1 19990107 (199906) EN

R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI

AU 705063 B 19990513 (199930)

JP 2000507818 W 20000627 (200036) 73

US 6254868 B1 20010703 (200140)

US 2003035800 A1 20030220 (200316)

EP 888125 B1 20040526 (200435) EN

R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE SI

DE 69729283 E 20040701 (200443)

US 2004258682 A1 20041223 (200504)

DE 69729283 T2 20050525 (200537)

ADT WO 9734632 A1 WO 1997-US4196 19970319; AU 9725318 A AU 1997-25318 19970319; EP 888125 A1 EP 1997-916787 19970319, WO 1997-US4196 19970319; AU 705063 B AU 1997-25318 19970319; JP 2000507818 W JP 1997-533585 19970319, WO 1997-US4196 19970319; US 6254868 B1 Provisional US 1996-13709P 19960320, WO 1997-US4196 19970319, US 1998-155107 19981117; US 2003035800 A1 Provisional US 1996-13709P 19960320, Cont of WO 1997-US4196

19970319, Cont of US 1998-155107 19981117, US 2001-894839 20010629; EP 888125 B1 EP 1997-916787 19970319, WO 1997-US4196 19970319; DE 69729283 E DE 1997-629283 19970319, EP 1997-916787 19970319, WO 1997-US4196 19970319; US 2004258682 A1 Provisional US 1996-13709P 19960320, Cont of WO 1997-US4196 19970319, Cont of US 1998-155107 19981117, Cont of US 2001-894839 20010629, US 2004-787378 20040227; DE 69729283 T2 DE 1997-629283 19970319, EP 1997-916787 19970319, WO 1997-US4196 19970319

FDT AU 9725318 A Based on WO 9734632; EP 888125 A1 Based on WO 9734632; AU 705063 B Previous Publ. AU 9725318, Based on WO 9734632; JP 2000507818 W Based on WO 9734632; US 6254868 B1 Based on WO 9734632; US 2003035800 A1 Cont of US 6254868; EP 888125 B1 Based on WO 9734632; DE 69729283 E Based on EP 888125, Based on WO 9734632; US 2004258682 A1 Cont of US 6254868; DE 69729283 T2 Based on EP 888125, Based on WO 9734632

PRAI US 1996-13709P 19960320; US 1998-155107 19981117; US 2001-894839 20010629; US 2004-787378 20040227

AB WO 9734632 A UPAB: 20050613

Monoclonal antibody (MAb), or a fragment, engineered to contain a glycosylation site in the non-Fc constant heavy or light chain region, is claimed. Also claimed is an isolated DNA molecule comprising: (a) Ab heavy chain gene, comprising a sequence in the CH1 region that, when the gene is coexpressed with a gene for an Ab light chain in a cell supporting glycosylation, will produce an Ab glycosylated in the CH1 region; or (b) Ab light chain gene, comprising a sequence in the constant K region that, when the gene is coexpressed with a gene for an Ab heavy chain in a cell supporting glycosylation, will produce an Ab glycosylated in the constant K region.

USE - The MAb (preferably humanised), or a fragment, can be used to diagnose or treat of B cell malignancies, e.g. non-Hodgkins lymphoma or chronic lymphocytic leukaemia.

ADVANTAGE - The glycosylation site allows a label or therapeutic agent of increased size to be conjugated to the carbohydrate moiety, without affecting the MAb's binding affinity or specificity.

Dwg.0/12